NEW JERSEY AIDS Line
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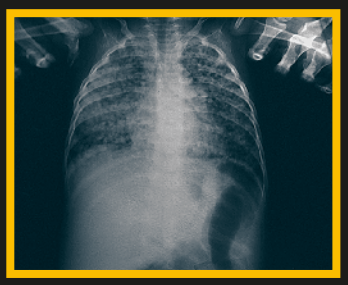
CE Continuing Education



CME/CE Article #1

Medical Monitoring Project

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MEDICAL MONITORING PROJECT

MMP is the most comprehensive project of its kind. It is unique in that it provides extensive clinical and behavioral information from patient samples carefully selected to represent everyone receiving medical care for HIV in the US. The findings will highlight disparities in care and services and advocate for additional resources.

HIV surveillance programs in the United States (US) collect information about persons who have received a diagnosis of HIV infection and AIDS. For example, the Centers for Disease Control and Prevention (CDC) estimates that more than 1.1 million people in the US are living with HIV infection. In 2010, an estimated 47,129 people were diagnosed with HIV infection in the 46 states with confidential name-based HIV infection reporting since at least January 2007. In that same year, an estimated 33,015 people throughout the US were diagnosed with AIDS.[1] What CDC doesn't know, or didn't know prior to 2008, was the health-related experiences and needs of this HIV-infected population:

- How many people living with HIV/AIDS are receiving care for HIV?
- How easy is it to access care and use prevention and support services?
- What needs of persons living with HIV/AIDS are not met?
- How is treatment affecting people living with HIV/AIDS?

The CDC implemented the Medical Monitoring Project (MMP) to answer these questions using a nationally representative study on people living with HIV who are receiving care in the US. The data from this project are critical to reduce HIV-related morbidity and mortality, to assess unmet medical and ancillary service needs, for program planning and to allocate services and resources. At a local level data from the MMP will be used to guide HIV prevention community planning groups, Ryan White CARE Act planning councils, providers of HIV care and other policy makers and service planners.

MMP in New Jersey

The New Jersey Department of Health (NJDOH) is collaborating with the CDC, the National Institutes of Health, and the Health Resources and Services Administration as one of 23 participating jurisdictions in the MMP. On June 1, 2013, the NJDOH will start the 5th year of a 5-year grant.

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NJ Health New Jersey Department of Health

CE CONTINUING EDUCATION

Recent Developments in Tuberculosis and Tuberculosis-HIV Co-Infection

Release Date: June 1, 2013 • Expiration Date: May 31, 2015 • Course Code: 15HC01 • Nursing credit for this activity will be provided through May 31, 2015

SPONSOR:

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GRANTOR ACKNOWLEDGEMENT:

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STATEMENT OF NEED:

Despite the fact that tuberculosis (TB) has become an increasingly uncommon disease in the United States, it still remains a public health problem of enormous importance, and this importance is amplified by the synergistic effects of latent TB infection (LTBI) in those who are HIV-infected (i.e., TB-HIV co-infection). TB contributes substantially to morbidity and mortality of people living with HIV who are foreign-born, who also comprise an increasing proportion of those newly diagnosed with HIV infection.

There have been important recent advances in tools to diagnose LTBI and active TB including interferon-gamma release assays (IGRAs). There are also new short course regimens available for the treatment of LTBI. However there have also been unforeseen challenges to treatment of LTBI and TB disease due to shortages of important anti-tuberculosis agents, including the current nationwide shortage of isoniazid (INH) tablets.

The greatest new challenge to recent progress in global control of TB has been the continuing emergence of multi-drug resistant (MDR) and extensively drug resistant (XDR) strains of TB. Treatment of drug resistant TB involves use of more prolonged, more toxic and less effective therapies and significantly increases the cost of TB care. The emergence of drug-resistant TB has spurred development and deployment of new, rapid tools for simultaneous identification of both TB disease and drug resistance, and has also sparked the development of new drugs for treatment of MDR strains.

TARGET AUDIENCE:

This activity is designed for physicians, nurses, social workers, health educators, and other health care professionals in New Jersey who are involved in the care of people with HIV.

METHOD OF PARTICIPATION:

Participants should read the learning objectives, review the activity in its entirety, and then complete the self-assessment test, which consists of a series of multiple-choice questions. Upon completing this activity as designed and achieving a passing score of 70% or more on the self-assessment test; participants will receive a letter of credit and the test answer key four (4) weeks after receipt of the self-assessment test, registration, and evaluation materials. This activity may also be completed online at http://ccoe.umdnj.edu/catalog/. Estimated time to complete this activity as designed is 1.00 hour for nurses, and 0.75 hour for physicians.

LEARNING OBJECTIVES:

Following completion of this activity, participants should be able to:

1. Describe the tools used to diagnose TB disease and LTBI.
2. Summarize the treatment options for LTBI.
3. Summarize the new tools for diagnosing and new drugs for treating MDR and XDR TB

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This activity is awarded 1.00 contact hour (60 minute CH).

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In order to help ensure content objectivity, independence, and fair balance, and to ensure that the content is aligned with the interest of the public, UMDNJ-CCOE has resolved all potential and real conflicts of interest through content review by a non-conflicted, qualified reviewer. This activity was peer-reviewed for relevance, accuracy of content and balance of presentation by Joanne Phillips, RN, MS.

Field test: This activity was pilot-tested for time required for participation by Bonnie R. Abedini, MSN, RN; David John Cennimo, MD; Jojy Cheriyan, MD, MPH, MPhil; Anna M. Haywood, RN, MSN; Mary C. Krug, RN, MSN, APN; Kinshasa Morton, MD; Shobha Swaminathan, MD; and Kara Winslow, BSN, RN.

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Disclosure Declarations: There were no relevant financial relationships to disclose reported by the activity directors, the author, planning committee members, the peer reviewer or field testers. However, the author's spouse, Jacqueline French, MD, received grant funding from the Milken Foundation, the Epilepsy Therapy Project, and NINDS. She serves as the president of the Epilepsy Study Consortium, a nonprofit organization. NYU receives a fixed amount from the Epilepsy Study Consortium towards Dr. French's salary for consulting and clinical trial-related activities. Dr. French receives no personal income for these activities. Within the past year the Epilepsy Study Consortium received payments from the following: Biotie, Cyberonics, Eisai Medical Research, Entra Pharmaceuticals, GlaxoSmithKline, Icagen, Inc., Johnson & Johnson, Mapp Pharmaceuticals, Marinus, Neurotherapeutics, Neuropace, NeuroVista Corporation, Ono Pharma USA, Inc., Lundbeck, Pfizer, Sepracor, Sunovion, SK Life Science, Supernus Pharmaceuticals, UCB Inc/Schwarz Pharma, Upsher Smith, Valeant, Vertex.

OFF-LABEL/INVESTIGATIONAL USE DISCLOSURE:

This activity provides an overview of Xpert MTB/RIF Assay, which — although endorsed by WHO — is not yet FDA approved. This activity also includes mention of delamanid, a drug for the treatment of MDR-TB that is currently in phase 3 trials. Delamanid is not yet FDA approved.

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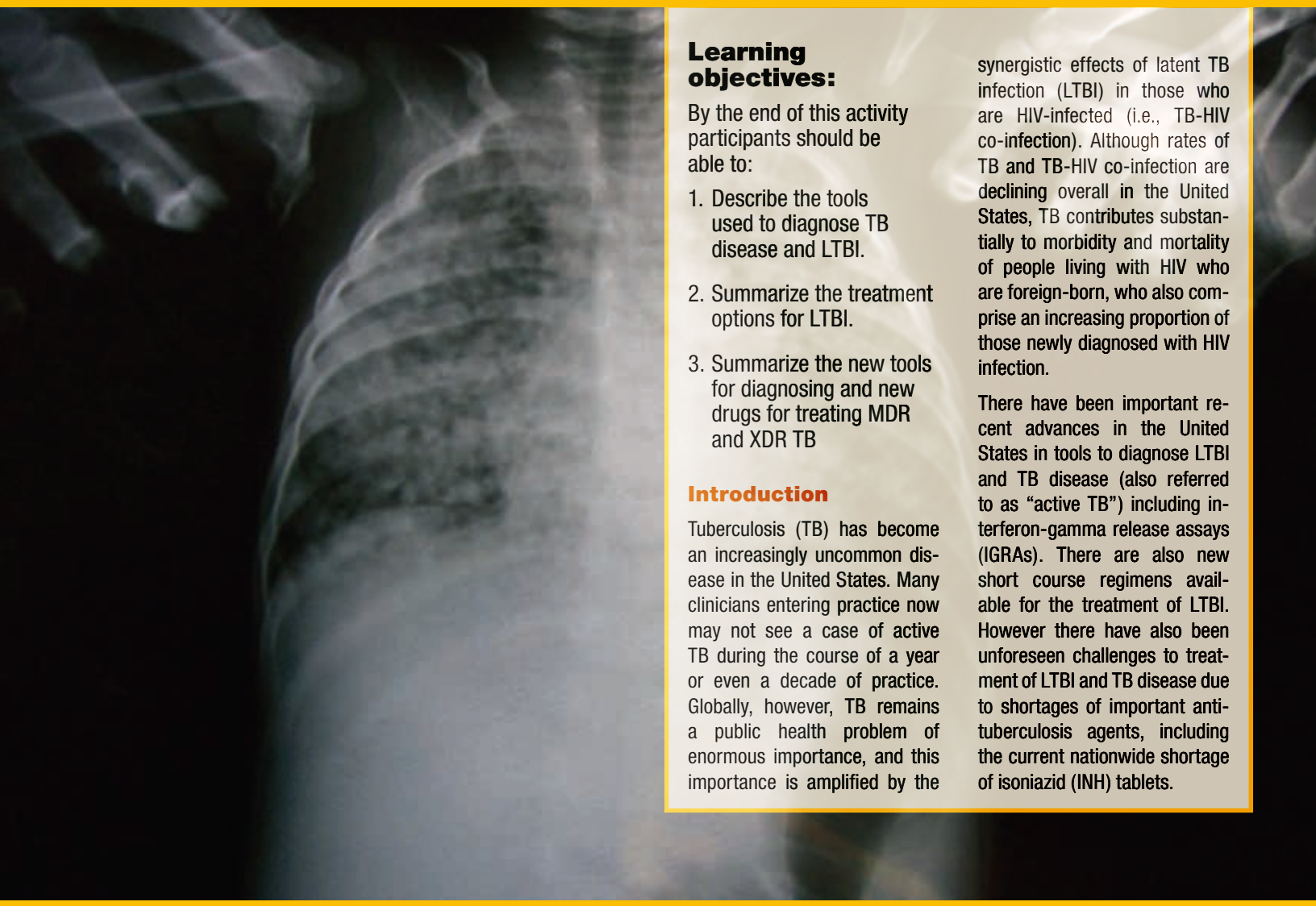
NEW JERSEY AIDSLine June 2013

Recent Developments in Tuberculosis and Tuberculosis-HIV Co-Infection

Henry Shalom Fraimow, M.D., Associate Professor of Medicine, UMDNJ-Robert Wood Johnson Medical School and Attending Physician, Cooper University Hospital



Learning objectives:

By the end of this activity participants should be able to:

1. Describe the tools used to diagnose TB disease and LTBI.
2. Summarize the treatment options for LTBI.
3. Summarize the new tools for diagnosing and new drugs for treating MDR and XDR TB

Introduction

Tuberculosis (TB) has become an increasingly uncommon disease in the United States. Many clinicians entering practice now may not see a case of active TB during the course of a year or even a decade of practice. Globally, however, TB remains a public health problem of enormous importance, and this importance is amplified by the synergistic effects of latent TB infection (LTBI) in those who are HIV-infected (i.e., TB-HIV co-infection). Although rates of TB and TB-HIV co-infection are declining overall in the United States, TB contributes substantially to morbidity and mortality of people living with HIV who are foreign-born, who also comprise an increasing proportion of those newly diagnosed with HIV infection.

There have been important recent advances in the United States in tools to diagnose LTBI and TB disease (also referred to as "active TB") including interferon-gamma release assays (IGRAs). There are also new short course regimens available for the treatment of LTBI. However there have also been unforeseen challenges to treatment of LTBI and TB disease due to shortages of important antituberculosis agents, including the current nationwide shortage of isoniazid (INH) tablets.

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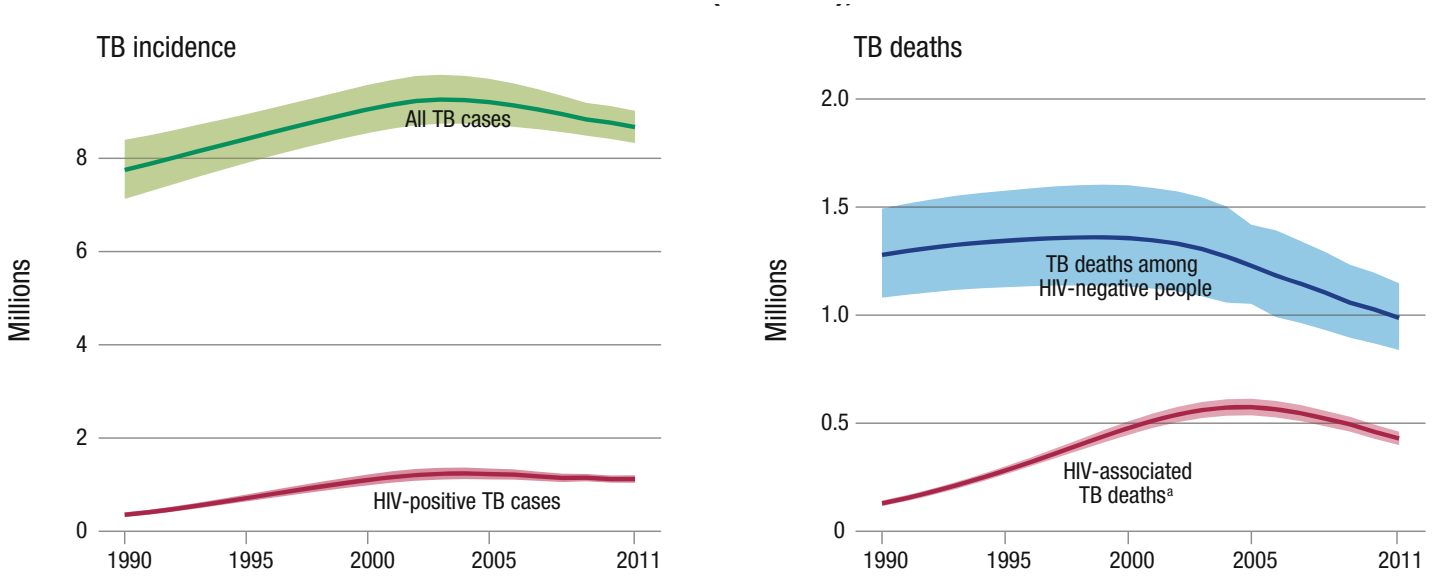
The greatest new challenge to recent progress in global control of TB has been the continuing emergence of multi-drug resistant (MDR) and extensively drug resistant (XDR) strains of TB. Such strains can be particularly lethal in individuals with advanced HIV disease. MDR and XDR strains are increasingly prevalent in many regions of the world, though they still remain relatively rare in the United States. Treatment of drug resistant TB involves use of more prolonged, more toxic and less effective therapies and significantly increases the cost of TB care. The emergence of drug-resistant TB has spurred development and deployment of new, rapid tools for simultaneous identification of both TB disease and drug resistance, and has also sparked the development of new drugs for treatment of MDR strains.

TB and TB-HIV co-infection: Where are we now?

The global incidence of TB, as well as TB-associated mortality, has continued to decline every year since 2006.[1] In 2011, the last year for which there is complete reporting data from the World Health Organization (WHO), there were an estimated 8.7 million new cases of TB and 1.4 million TB-related deaths, an ongoing decrease from prior years (see Figure 1). Due to tremendous efforts by WHO and its many governmental and philanthropic partners, rates are now falling in most developing countries, including the many countries in sub-Saharan Africa that for the past 2 decades have had the highest burden of TB and HIV-TB co-infection.

The global incidence of TB, as well as TB-associated mortality, has continued to decline every year since 2006.

Figure 1: Estimated absolute numbers of global TB cases and deaths (in millions) 1990–2011



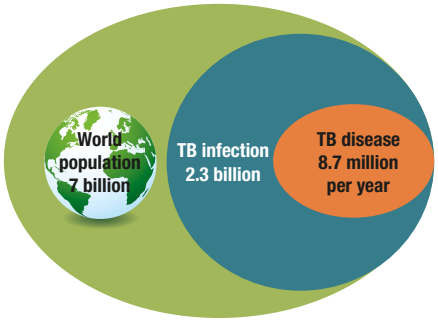
[a] HIV-associated TB deaths are classified as HIV deaths according to ICD-10.

World Health Organization. *Global Tuberculosis Report* 2012. Geneva, Switzerland: WHO. 2012. Accessed at http://www.who.int/tb/publications/global_report/en/.

Despite these successes, the global burden of TB, and of TB-HIV co-infection remains staggering. Thirteen percent of new TB cases in 2011 were in people who were co-infected with HIV; this figure is as high as 80% in the high TB/high HIV burden countries of southern Africa. One quarter of global HIV deaths are attributable to TB, and mortality rates for those with TB disease are 4-fold higher for HIV-infected than uninfected individuals. HIV infection and TB act synergistically to increase the burden of disease in co-infected populations.

One third of the world's population is infected with TB (Figure 2). The vast majority have LTBI. These individuals are neither sick nor capable of transmitting disease, but have the potential to progress from latent to active TB. Immunosuppression from advanced HIV infection is the strongest known risk factor for progression from latent to active TB, increasing the average risk of progression from a *total lifetime risk* of 5–10% to an *annual risk* of 7–10%.[2,3] Strategies for management of this risk in those with HIV infection vary significantly in low TB burden countries — such as the United States and Western Europe — from those employed in high TB burden, resource-limited settings.[4]

Figure 2: Estimated number of persons infected with TB and with TB disease, globally, 2012



Source of data: World Health Organization. *Global Tuberculosis Report* 2012. Geneva, Switzerland: WHO. 2012. Accessed at http://www.who.int/tb/publications/global_report/en/

The strategy in low TB burden countries is to focus on both identification and treatment of patients with TB disease and identification and treatment of LTBI to prevent progression to TB disease.[5] The United States CDC guidelines prioritize those who are HIV-infected — in addition to other high priority groups — for LTBI treatment. Other priority groups include those who are immunosuppressed for other reasons, recent contacts of a TB case, and those with fibrotic changes on chest radiograph consistent with old TB.[6]

In high TB burden, resource-limited settings, strategies for HIV-infected individuals are directed at:

1. Use of simple symptom-based screening tools to identify and then treat the large number of patients who may be already sick with TB.
2. Universal treatment for LTBI in those who are also HIV-infected who have no evidence of active TB, using regimens such as 6 months, or even as long as 3 years, of INH.[4]

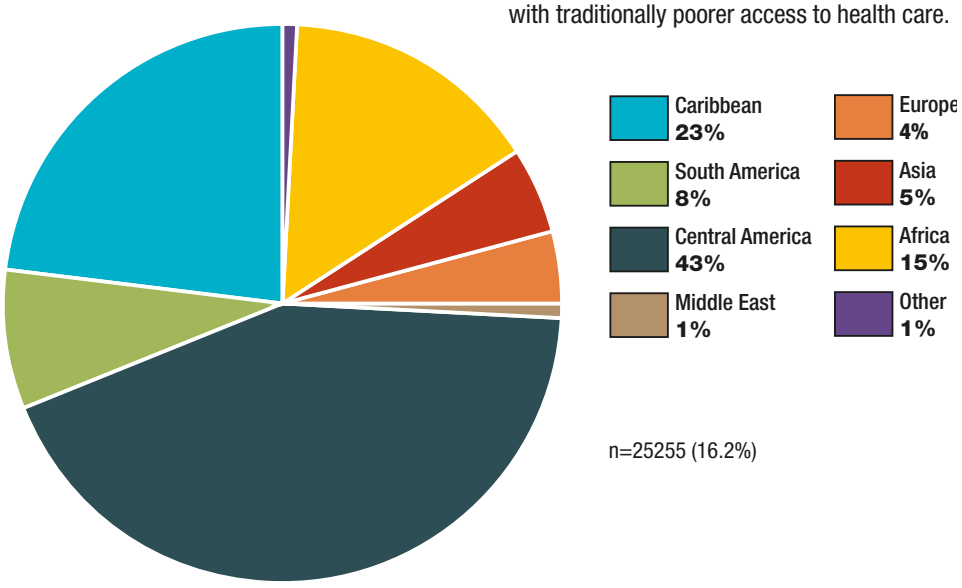
Another component of TB control in HIV-infected individuals is treatment with antiretroviral therapy (ART). The risk of TB disease decreases with initiation of ART and consequent increase in CD4 cell counts.[7] However, the barriers to universal availability of ART in many parts of the world remain substantial.

From global to local: TB and HIV-TB co-infection in the United States

There were less than 10,000 new cases of TB reported in the United States in 2012, the 20th consecutive year of declining cases. The 2012 TB incidence is an all-time low of 3.2 new cases per 100,000 population.[7] For comparison, new case rates in 2011 were 75 cases per 100,000 in China, 181 per 100,000 in India, and 995 per 100,000 in South Africa.[1] Approximately 7.7% of new TB cases in the United States were in individuals co-infected with HIV, but the rate of co-infection increases to 10% in the 25–44 year age cohort.

Rates of screening for HIV infection among new TB cases continue to improve: 90% of new TB cases in the 25–44 year age cohort were HIV tested in 2011. Although mortality among patients with TB and HIV has decreased substantially in the United States since ART became widely available and the number of HIV co-infected TB cases in the United States is relatively low, mortality of co-infected patients is 4-fold higher than for un-infected. This is similar to TB mortality differences between HIV-infected and uninfected individuals from other parts of the world.[8]

Figure 3: New HIV infections in persons born outside the United States and region of origin, 2007–2010



Source of data: Prosser AT, Tang T, Hall I. HIV infection in persons born outside the United States. *JAMA* 2012; 308(6):601-607.

The other significant trend among TB cases in the US is the steadily increasing proportion of cases among foreign-born individuals.[9] Sixty-three percent of TB cases in 2012 were diagnosed in foreign-born individuals, and the states with higher than the national average TB incidence rates, including New Jersey, are also those with high numbers of foreign-born individuals. Seventy-five percent of the 331 new cases of TB in New Jersey in 2011 were in individuals born outside of the United States. As rates of TB in the United States decline, transmission of TB in the US will continue to decrease, but immigrants from high TB burden countries will continue to be at risk for progression from LTBI to active TB. This risk is particularly amplified in immigrants who are also HIV-infected.

Until recently, there has been little information available on country of origin of those newly diagnosed with HIV infection in the United States. A recently published study of new HIV cases from 2007–2010 found that 16.2% were born outside of the United States. Of the 81% of these for whom country or region of birth was available, most were from regions of the world where TB rates are much higher than in the United States: 15% were from Africa and 51% from Central or South America (Figure 3).[10] Thus despite an overall decline in TB in the US, TB and HIV-TB co-infection will continue to be issues among immigrant communities, groups with traditionally poorer access to health care.

What's new in the diagnosis of LTBI and TB disease?

There are two types of tests available for screening for LTBI and active TB:

- The tuberculin skin test (TST) using purified protein derivative (PPD)
- Interferon-gamma release assay (IGRA) blood tests. Currently available IGRA tests include the QuantiFERON® TB-Gold in-Tube and the T-Spot.TBTM Assay.

Both the TST and IGRA are approved by CDC for diagnosis of LTBI and are considered to be equivalent in most populations, including HIV-infected individuals.[11] Comparison of TST and IGRA and differences between IGRA tests are shown in Table 1.

Table 1: Comparison of tests available for diagnosis of LTBI

Test	TST	QuantiFERON® TB-Gold in-Tube	T-Spot.TB™ Assay	Comments
Minimum number of visits to complete testing	2 or more	1	1	IGRA preferred when with low rates of return
Method	Injection into skin	Blood draw	Blood draw	
What the test measures	Induration after intradermal injection of 5 units of tuberculosis purified protein derivative (PPD)	Interferon Gamma concentration in blood in response to TB antigens ESAT 6 and CFP-10	Number of Interferon Gamma producing cells (spots) in response to TB antigens ESAT 6 and CFP-10	Inter-reader variability of TST
Cross reactivity with BCG	Yes	No	No	IGRA preferred for BCG vaccinated
Cross reactivity with non-tuberculous mycobacteria	Yes	Less likely	Less likely	IGRA can be positive with *M.kansasii, M.marinum, M.szulgaii*
Minimum time to results	48–72 hours	24 hours	24 hours	May be much longer depending on access to laboratory
Sample processing complexity	None	Moderate	High	More potential errors in collecting, transporting and processing IGRAs
Laboratory support required	No	Yes	Yes	More potential errors in collecting, transporting and processing IGRAs
Can be used in diagnosis of active tuberculosis	Yes	Yes	Yes	Sensitivity of all tests only around 70–80%, decreased sensitivity in immunosuppressed e.g., HIV infection with CD4 < 200
Can be for diagnosis of LTBI	Yes	Yes	Yes	Limited IGRA data in children < 5 years of age
Can be used for serial testing eg HCW, nursing home residents	Yes	Yes	Yes	IGRA tests may demonstrate higher than expected "conversion" rates

Advantages of the IGRA:

- IGRAs measure release of interferon-gamma from immune cells in blood specimens in vitro that are exposed to TB antigens. IGRA tests eliminate the need for patients to return to have their tests read, so often the testing protocol can be completed in a single visit. Thus IGRA tests are preferred in populations with traditionally low rates of return for reading of TSTs.[11]
- Test results are unaffected by history of prior vaccination with bacille Calmette-Guérin (BCG) vaccine. BCG is administered to infants in high TB burden regions of the world to prevent overwhelming TB disease in young children. Effects of BCG vaccination on TST wane over time, but can still occasionally produce false positive TST results in individuals who do not have LTBI. Routine use of IGRA assays for evaluation of foreign-born individuals with positive TST has significantly decreased the number of false positives, thereby decreasing the number of individuals qualifying for LTBI treatment in many TB programs in the United States.

TST and people with HIV:

- TST remains the preferred test for children less than 5 years of age.
- Although some studies have suggested that IGRA tests may be more likely to be positive

with lower CD4 counts compared to TST (low CD4 counts are associated with increases in false-negative TST results), recent meta-analyses have confirmed the limitations of both TST and IGRA in individuals with lower CD4 counts, especially those under 200 cells.[12] Thus HIV-infected patients with low CD4 counts and negative TB screening tests should be considered as "TB status indeterminate" rather than uninfected. The criteria for a positive TST in HIV-infected individuals is 5 mm of induration.

There are still some situations where data on use of IGRAs is insufficient or where emerging data suggest that IGRAs may have significant limitations, such as use in serial testing of healthcare workers.[13] Studies of serially tested healthcare workers have found both high rates of IGRA conversion and subsequent apparent reversion to negative, and overall much higher rates of conversion than from concordantly administered TST. Thus although TST and IGRA assays may be equivalent for use as tests for diagnosis of LTBI and TB disease and for contact investigations, the data for serial use of IGRA assays compared to TST remains more limited.

Shortage of TST test antigens: Another issue in testing for LTBI is the current nationwide shortage of TST test antigens that was recently reported by the CDC.[14] One PPD TST product, TUBERSOL®, is reported to be unavailable until at least the end of May 2013, and shortages of TUBERSOL® have produced secondary shortages of the APLISOL®, the other FDA licensed PPD skin test product. The expected duration of the shortage is unknown.

Recommendations by the CDC for dealing with shortages of the TUBERSOL® product include:

1. Using IGRA assays in situations where the two tests are equivalent or where IGRAs are preferred
2. Allocating use of TSTs to highest priority indications, as determined by public health authorities, such as TB contact investigations. This might mean deferring the testing of some persons with lower priority indications
3. Using APLISOL® instead of TUBERSOL® if available

Treatment of LTBI in the United States

There are four acceptable, CDC/USPHS approved regimens in the United States for the treatment of LTBI (Table 2).

- **9 months isoniazid (INH):** The longstanding standard of treatment in the United States has been 9 months (270 doses) of INH by daily, self-administered therapy. This regimen can also be given twice weekly, but only if administered by directly observed therapy (DOT).
- **6 months INH:** 6 months (180 doses) of INH is estimated to be approximately 75-80% as effective as 9 months and is an acceptable alternative.
- **4 months rifampin (RIF):** RIF daily therapy for 4 months (10 mg/kg up to 600 mg), or for 6 months in children, is an alternative to INH. Though data for the RIF regimen is more limited, in some comparative studies completion rates have been higher than with 9 months of INH.[15] This regimen is also preferred where there is suspicion of INH resistant disease and in individuals at higher risk for or who have demonstrated toxicity from INH. There is less data for RIF regimens in children, thus INH remains the preferred regimen in children under age 11. The other major issues for RIF regimens are related to drug interactions. RIF is a potent cytochrome 3A4 inducer, resulting in increased metabolism and decreased levels of many co-administered drugs. This is a major issue in co-infected patients also on ART, particularly with protease inhibitors but also with other ART drug classes, where decrease in ART levels, could potentially result in failure of ART therapy. Another rifamycin, rifabutin (RBT) is a less potent inducer of cytochrome 3A4 and can potentially be used in some instances where RIF cannot be used. Updated information on co-administration of rifamycins and ART is available in the Department of Health and Human Services Guidelines for the use of antiretroviral agents in adults and adolescents.[16]
- **12 weeks INH + rifapentine (RPT):** The recently completed CDC-sponsored PREVENT-TB trial compared a novel regimen of once weekly INH plus the longer half-life rifamycin drug RPT administered by DOT for 12 weeks against the standard regimen of 9 months of INH in more than 8,000 patients with LTBI at risk for progression to TB disease.[17] The major conclusions of this study were that the 12 week regimen was as safe and as effective in preventing development of TB disease as the standard regimen; adherence and completion rates for the 12 week regimen were higher (82% vs 69%). This study did include HIV-infected individuals, but not those on ART. The overall rates of discontinuation of therapy due to suspected drug toxicity were similar for both regimens, but toxicity profiles were somewhat different, with higher rates of hepatotoxicity in the INH arm but higher rates of possible hypersensitivity reactions in the combination therapy arm.

Although it had significant advantages — particularly the higher rates of completion — there were practical limitation to the routine use of the 3 month INH-RPT regimen. Specifically, the INH-RPT regimen needed to be DOT, rather than self-administered. Additionally, INH-RPT is currently not recommended for the following patients:

- Children aged <2 years, because the safety and pharmacokinetics of RPT have not been established for them
- HIV-infected patients receiving ART, because the drug interactions have not been studied (studies looking at interactions of INH-RPT with some antiretroviral agents are ongoing)
- Pregnant women or women expecting to become pregnant during treatment, because safety in pregnancy is unknown
- Patients who have LTBI with presumed INH or RIF resistance[18]

Table 2: Current options for treatment of latent TB infection

Drug(s)	Duration	Interval	Dose	Minimum.# of Doses	Comments
Isoniazid	9 months	Daily	Adult: 5 mg/kg Children 10-20 mg/kg 300 mg maximum	270	Preferred regimen for children 2-11 and for HIV-infected on ART
		Twice weekly	Adult 15 mg/kg Children 20-40 mg/kg 900 mg maximum	76	Must be given by DOT
Isoniazid	6 months	Daily	Adult: 5 mg/kg Children 10-20 mg/kg 300 mg maximum	180	Estimated 75-80% as effective as 9 months of INH
		Twice weekly	Adult 15 mg/kg Children 20-40 mg/kg 900 mg maximum	52	Must be given by DOT
Rifampin	4 months	Daily	10 mg/kg, maximum 600 mg maximum	120	6 months for children/adolescents Preferred if suspected INH resistance
Isoniazid plus Rifapentine	3 months	Weekly	Adults and Children > 12 INH: 15 mg/kg rounded up to the nearest 50 or 100 mg 900 mg maximum RPT: 10.0–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥50.0 kg: 900 mg	12	Must be given by DOT Not currently recommended for: age < 2, Pregnancy, HIV on ART, suspected resistance to either INH or RIF

The choice of LTBI treatment regimen is based on a variety of factors:

- **Likelihood of completion:** The most important factor is likelihood of completion of therapy. There is no individual or public health benefit to initiation of an LTBI regimen that is not completed.
- **Risk of toxicity:** Risk of toxicity, especially INH hepatotoxicity in those with underlying liver disease, as well as concern for drug-drug interactions.
- **Susceptibility issues:** Regimens in contacts should be based on susceptibility of the source patient, if available. Where there is no data available, there may be benefits to use of RIF regimens for treatment of LTBI in individuals from regions with highest rates of INH resistance.[19] Contacts of MDR TB cases should be managed with expert consultation.

Another unforeseen complication to treatment of LTBI is the current national shortage of INH tablets first reported by the CDC in November 2012 that has impacted on many regional TB jurisdictions throughout the United States.[20] The anticipated duration of the current shortage is unknown. Current priorities for use of available supplies of INH as outlined in a recent CDC Health Advisory include treatment of patients with active TB disease, treatment of LTBI in individuals diagnosed during contact investigations of active cases, and treatment of LTBI in those at highest risk of developing TB disease (e.g., HIV-infected patients) and those at highest risk for developing severe disease (children younger than 5 years of age).[21]

The New Jersey Department of Health Division of HIV, STD and TB Services has also issued guidance for priorities for use of remaining supplies of INH in New Jersey during the period of shortage (Table 3). Highest priorities include:

1. Treatment of patients with confirmed or suspected TB
2. Treatment of LTBI in contacts of cases resistant to RIF but not INH
3. Children weighing less than 15 kg
4. Treatment of LTBI in HIV-infected patients where RIF cannot be used

Alternatives to INH regimens in those without contraindications would be 4 months of daily RIF. RIF daily for 6 months can be used in children, but INH is still the preferred regimen for children less than 11 years of age. Three months of INH-RPT has the advantage of using significantly less INH (thirty six 300 mg tablets for the average adult) than the 270 doses necessary in a 9 month INH regimen.

Table 3: Priorities for use of isoniazid during the isoniazid shortage (New Jersey)

	Indication	Comments
Highest Priority for use of INH	Patients on treatment for confirmed or suspected active TB	If available, rifamate (INH plus RIF) can be used in preference to INH for patients on treatment regimens containing INH plus RIF
	Treatment of LTBI in contacts with INH susceptible, rifampin resistant disease	
	Treatment of LTBI in children < 15 kg	
	Treatment of LTBI in HIV-infected individuals where RIF cannot be used due to drug interactions with ART	Can use RIF if not on ART Can use rifabutin in some instances where RIF cannot be used, seek expert consultation
Priorities for Treating LTBI with alternative to INH*	Contacts to active TB	Regimen based on susceptibility of index case, if available
	Patients with increased risk of progression from LTBI to active TB	For example: HIV infection and other severe immunosuppression, patients receiving TNF inhibitor therapy, patients with radiographic evidence of old healed TB, recent immigrants/refugees, other high risk
	Patients with higher risk of severe disease if they progress from latent to active TB	
	All other patients with LTBI	Consider deferring LTBI therapy in those where risk of progression to active TB is low; however must ensure mechanisms are in place to contact these individuals when drug supplies are no longer an issue
*Includes: RIF x 4 months in adults or x 6 months in children Once weekly INH plus rifapentine x 3 months by DOT, as this regimen uses much less INH		

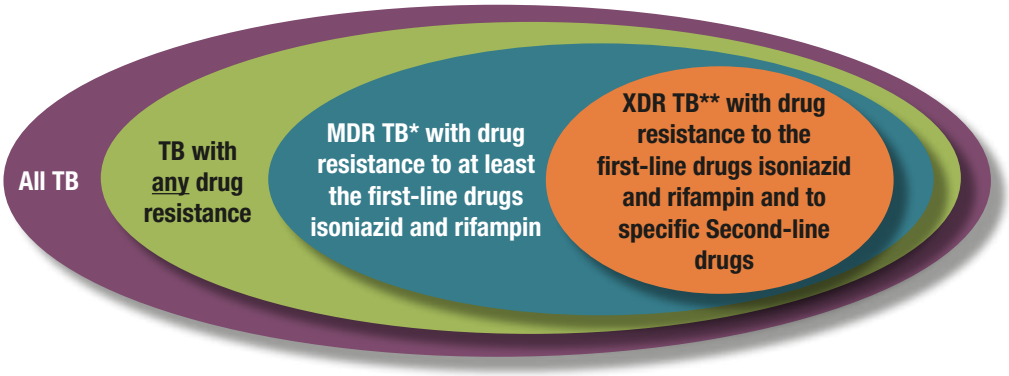
MDR TB and beyond

The greatest current threat to progress in the global control of TB is the continuing emergence of MDR TB.[22] Multi-drug resistance is defined as TB strains that are resistant to the two most important first line TB drugs: INH and RIF. These strains may also be resistant to other first line agents.[22] A subset of MDR includes XDR, or extensively-drug resistant TB, defined as strains that are resistant to INH and RIF but also resistant to the most effective second line agents including fluoroquinolones and at least one of the second line injectable agents (Figure 4). Other terms that have been used for even more resistant isolates include "extremely drug resistant" and "completely drug resistant", but these are not yet officially defined or accepted terms. The more first and second line drugs to which an M. TB strain is resistant, the more complicated, more prolonged, potentially more toxic, and less effective the treatment compared to that for drug susceptible disease.

Figure 4: Drug-resistant, MDR and XDR TB

Multidrug-resistant (MDR) TB strains are resistant to isoniazid and rifampin

Extensively drug-resistant (XDR) TB strains are resistant to isoniazid and rifampin, plus fluroquinolones and 1 of the 3 injectable second-line drugs



* Often resistant to additional drugs

** Resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)

Source: CDC. *Core Curriculum in Tuberculosis.* What the clinician should know. 2011. Accessed at http://www.cdc.gov/tb/publications/slidesets/corecurr/default.htm April 17, 2013.

Primary drug resistance occurs when an individual is initially infected with a strain of M. TB already expressing drug resistance. Secondary or acquired drug resistance occurs as a consequence of incorrectly administered therapy, which can occur as a consequence of errors in either the choice of therapy or the supervision of therapy such as use of self-administered therapy rather than DOT. Acquired drug resistance is often a consequence of weak TB control programs.

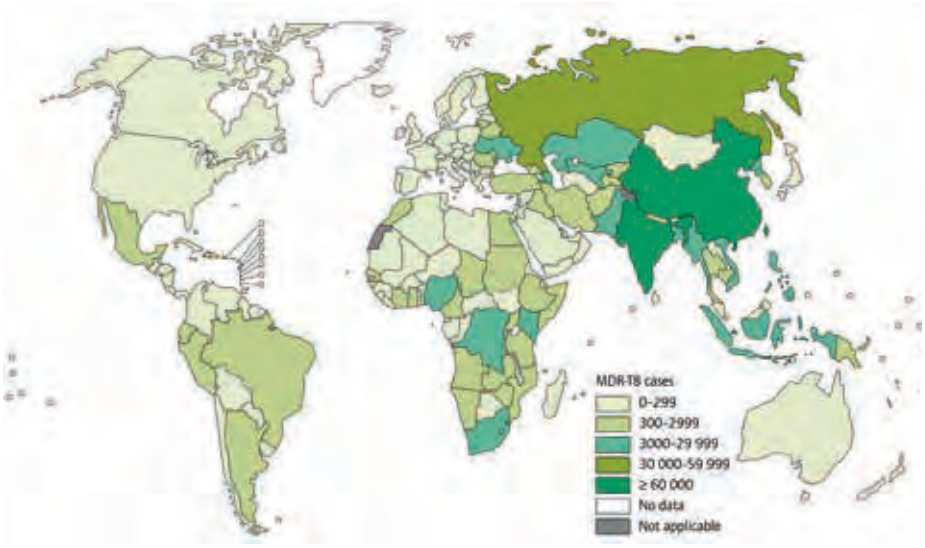
WHO estimates that there were 0.4–0.5 million cases of MDR TB worldwide in 2011, including 3.7% of all new cases and 20% of retreatment cases.[1] However, these estimates are limited by the lack of routine availability of drug sus-

ceptibility testing (DST) in many regions of the world and could be significant underestimates. Only 4% of new TB cases worldwide had drug-susceptibility testing reported in 2011; the proportion of relapsed cases with reported susceptibility testing were significantly higher, but still far below WHO targets.[1]

In terms of case numbers, the highest total burden of MDR cases are from the high TB burden and high population countries India and China (Figure 5A). One recent study from China suggests that rates are much higher than had been anticipated, with MDR in nearly 1 in 10 cases, including 5.7% of new and 25.6% of re-treatment cases, with an estimate of 110,000 MDR cases and 8,200 XDR cases in 2007.[23]

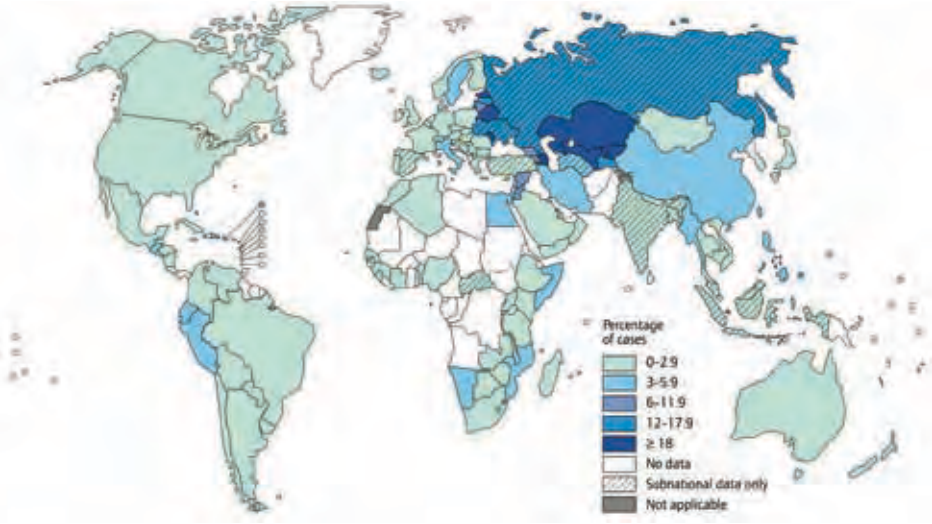
However, the highest rates of MDR and XDR disease are from Eastern Europe, particularly states of the former Soviet Union such as Belarus, Estonia, Kazakhstan and Kyrgyzstan (Figure 5B). Recently reported rates of MDR among newly diagnosed TB cases in some of the former Soviet states are as high as 30%, with rates of more than 50% among retreated patients.[1]

Figure 5A: MDR cases estimated to occur among notified pulmonary TB cases, 2011



Source: http://www.who.int/tb/challenges/mdr/drs_maps.pdf Accessed April 20, 2013.

Figure 5B: Percentage of new TB cases with MDR TB, 2011 (or most recent year for which data is available)



Source: http://www.who.int/tb/challenges/mdr/drs_maps.pdf Accessed April 20, 2013.

MDR TB and XDR TB are both reported in the United States and although case numbers remain relatively low, the rates are increasing. In 2011, the most recent year for which there is full reporting, there were 127 cases of MDR TB (1.6% of all cases) in the United States, including 6 cases of XDR. Foreign-born persons accounted for 109 (85.8%) of the 127 MDR TB cases in 2011. The percentage of MDR TB cases among persons without a previous history of TB was 1.3% in 2011. For persons with a previous history of TB, the percentage with MDR TB was 8.2% in 2011.[8] There were 8 MDR TB cases reported from New Jersey in 2011, representing 2.4% of TB cases.

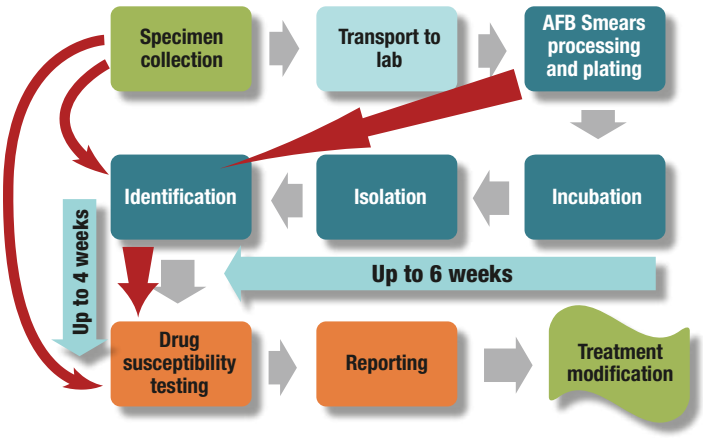
The challenge of MDR TB: new diagnostics and new drugs

Improvements in the diagnostic capability for rapid detection of MDR strains are required to address the challenge of MDR TB.[24,25] Traditional smear and culture based strategies for detection of drug resistance, which have not dramatically changed in the past 30 years, are slow, laborious and resource intensive, and not readily applicable to resource-limited high TB-burden regions (Figure 6). Currently in the United States it might take up to 3–4 months until diagnostic sensitivity test (DST) results are available to guide treatment, during which time patients may be treated with a totally in-

effective therapy, or potentially develop further resistance while on an only partially effective regimen with a single active agent. In settings without access to DST results, disease progression on treatment might be the only indicator of a multi-drug resistant isolate.

In the past five years, there has been major progress in the development of diagnostics for TB.[24] Some of this progress has been in enhancements of traditional tools such as improvements in microscopy, culture systems, species identification and susceptibility methodology and improvements in access to these tools in high TB burden regions. However, the "holy grail" of TB diagnostics is development of simple, rapid, point of care testing that permits direct detection of M. TB in clinical specimens as well as detection of resistance to the first line anti-TB agents.[24]

Figure 6: Processing of mycobacterial specimens and opportunities for improved efficiency



Xpert MTB/RIF assay: One major advance in TB diagnostics has been the development of the Xpert MTB/RIF assay. This assay was developed by Cepheid, using a diagnostic platform initially established for detection of other infectious diseases such as anthrax, in partnership with the Foundation for Innovative New Diagnostics (FIND) and the University of Medicine and Dentistry of New Jersey with support of the National Institute of Health.[25] This testing platform uses molecular beacon technology combined with polymerase chain reaction (PCR) in a self-contained modular system. Optimally, this self-contained, modular system could be used by workers with limited technical skills and presents low risk of cross-contamination of samples. The test identifies the presence of M. TB DNA and also detects mutations in the core region of the M. TB RNA polymerase subunit B (rpoB) gene.[26] 95% of mutations conferring RIF resistance are found in this region of the rpoB gene. The Xpert MTB/RIF assay was initially endorsed by WHO in 2010 and subsequently strongly recommended by WHO as the initial diagnostic test in individuals suspected of having either MDR TB or HIV-associated TB[27]. The Xpert MTB/RIF assay has been incorporated into national guidelines in a third of countries world-wide, including the majority of high burden countries.

Using assessment from multiple pooled trials, a single Xpert MTB/RIF test will detect 99% of smear positive and approximately 75% of smear negative pulmonary TB, with markedly decreased time to diagnosis compared to liquid or broth culture.[25] The assay also appears to have reasonable diagnostic efficacy in populations traditionally difficult to diagnose by sputum smears, such as children. The performance of Xpert MTB/RIF is also being evaluated for gastric aspirates and a variety of other non-pulmonary specimens. The sensitivity for detection of RIF resistance is also quite high, but there have been reports of RIF resistance that were not subsequently confirmed by standard drug susceptibility tests.[24, 25]

Despite the achievements of the Xpert MTB/RIF system, it still does not fulfill all of the criteria for an ideal TB diagnostic test:

- **Cost:** Although cheaper on a per test basis than traditional culture and susceptibility testing, the costs for the testing platform and testing modules are still higher than acceptable for routine use in resource-limited regions. To permit more rapid implementation of the test into high TB burden regions, subsidized cost for this test were negotiated initially by FIND, with subsequent funding provided by the President's Emergency Plan for AIDS Relief, the US Agency for International Development, UNITAID, and the Bill and Melinda Gates Foundation.
- **Computer hardware/skills/infrastructure:** Other practical limitations to "point of care" implementation of Xpert MTB/RIF in peripheral laboratories include issues with computer hardware, computer training skills and need for continuous electrical power and air conditioning. Developments of other, simpler, less technologically cumbersome tests are ongoing.

Molecular detection of drug resistance (MDDR): For rapid susceptibility testing for culture confirmed disease when resistance is suspected, the CDC MDDR service provides molecular assays for rapid detection of resistance to first line anti-tuberculous agents, as well as fluoroquinolones, injectable agents and some other 2nd line drugs. Testing is available on request through the CDC.[28] Molecular testing for drug resistance in New Jersey is also available through the Public Health Research Institute TB Center in Newark, New Jersey.

In addition to new diagnostics for more rapid identification of MDR infections, advances in treatment regimens are also desperately needed for treatment of MDR infections.[23, 29] These include both introduction of new effective drugs and assessment of combinations that permit shorter course treatment for MDR disease. There has been tremendous progress in expanding the pipeline of new drugs active against TB, including MDR TB, in the past 5 years with a number of compounds in phase 1 and 2 and phase 3 trials. One of these, bedaquiline (TMC207) (brand name Sirturo™), recently became the first new FDA approved drug developed exclusively for TB drug in four decades.[30] Bedaquiline is a diarylquinoline that inhibits ATP Synthase, and was developed for MDR TB jointly by Janssen and the Global TB Alliance. The FDA approval for this drug was not based on outcome of treatment, but rather on the basis of a surrogate marker: time to sterilization of sputum cultures in patients on an MDR TB regimen with or without bedaquiline. Additional clinical trials are ongoing. CDC is currently working with State and other regional TB programs to establish both criteria for use of the drug and systems to ensure distribution in situations where it would be indicted. Toxicities of bedaquinil include QT prolongation (i.e., prolongation of the QT internal as it appears on the electrocardiogram), for which the drug has a black box warning, as well as hepatotoxicity, nausea and arthralgias.[29]

Another novel agent that has completed phase 2B trials for treatment of MDR TB and is now in phase 3 studies is delamanid (OPC-67683), a nitro-dihydro-imidazooxazole that inhibits mycobacterial mycolic acid synthesis. In studies where delamanid was added to standard therapy for the first 2 months for MDR pulmonary TB, sputum sterilization rates were higher in patients who received delamanid.[31] The optimal strategies use of these and other new anti-tuberculous agents for patients with MDR and XDR TB is being evaluated.

Summary

TB remains an important disease worldwide and, despite decreasing case numbers, will continue to be an issue in the United States, especially in foreign-born individuals. Ongoing global challenges to control TB include TB and HIV co-infection and the emerging problem of MDR. There have been advances in diagnostic tools and treatments available for LTBI, and development of new tests and drugs for TB disease including MDR infection. There have also been unanticipated obstacles for treatment of LTBI and TB disease in the United States with the ongoing shortages of TST testing agents and shortages of INH. ❖

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Recent Developments in Tuberculosis and Tuberculosis-HIV Co-Infection

POST TEST — Page 1 of 1

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Questions refer to the content of the article. To receive CME/CE/CEU credit: complete exam, registration, and evaluation forms on-line at http://ccoe.umdnj.edu/catalog/ or fill in the forms on the following pages, and mail or fax to UMDNJ-CCOE (see Registration Form).

1. Which of the following is true:
   A. The global incidence of TB and TB-associated mortality have declined every year since 2006
   B. Although the global incidence of TB has increased, TB-associated mortality has declined since 2006
   C. Both global incidence of TB and TB-associated mortality have increased since 2006
   D. Although the global prevalence of TB has declined, TB-associated mortality has increased every year since 2006

2. What proportion of the world's population is infected with TB (either LTBI or active TB)?
   A. 1/20th
   B. 1/10th
   C. 1/5th
   D. 1/3rd

3. In 2012, what percentage of the United States' TB cases was diagnosed in foreign-born individuals?
   A. 23%
   B. 43%
   C. 63%
   D. 83%

4. You work in the Occupational Medicine Department at UMDNJ where you are responsible for pre-employment screening of applicants. Alice, who has been newly recruited as a nurse, was born in Jamaica. She is 48 years old, HIV-negative, and has lived in the United States since she was 25 years old. She's quite sure that she received BCG vaccination at birth. According to CDC guidelines, which would be the preferred test(s) to screen Alice for LTBI?
   A. TST
   B. IGRA
   C. IGRA and, if positive, TST
   D. Two step testing using the QuantiFERON® TB-Gold in-Tube followed by the T-Spot.TBTM Assay

5. Emil is HIV-infected with a CD4 count of 150. If his TST was negative, you would consider him:
   A. Likely uninfected with tuberculosis
   B. Likely infected with tuberculosis (as the IGRA should have been used)
   C. Likely infected with tuberculosis (as all people with HIV should be routinely treated for LTBI in the first year after diagnosis)
   D. TB status indeterminate

6. CDC reported a nationwide shortage of a TST test antigens called TUBERSOL®. Which of the following is NOT recommended to deal with shortages of the TUBERSOL product?
   A. Allocate use of TSTs for those who are highest priority; and deferring the testing of those who are lower priority
   B. Use APLISOL® instead of TUBERSOL® if available
   C. Use IGRA test where either TST and IGRAs are equivalent or where IGRAs are preferred
   D. Identify a reputable supplier in Canada, where there is currently no shortage

7. Which of the following is NOT one of the approved regimens in the United States for the treatment of LTBI?
   A. 9 months isoniazid
   B. 2 months rifampin + pyrazinamide
   C. 4 months rifampin
   D. 12 weeks isoniazid + rifapentine

8. Given the shortage of INH tablets, the New Jersey Department of Health Division of HIV, STD and TB Services has issued guidance for priorities for use of remaining supplies of INH in New Jersey during the period of shortage. Which of the following groups are NOT considered highest priority?
   A. Treatment of patients with confirmed or suspected TB
   B. Treatment of LTBI in all contacts
   C. Children weighing less than 15 kg
   D. Treatment of LTBI in HIV infected patients where RIF cannot be used

9. One of the major recent advances in TB diagnostics has been the development of the Xpert MTB/RIF assay. Why is the Xpert MTB/RIF assay so important?
   A. It was developed by a consortium that included UMDNJ
   B. It was endorsed and recommended by the World Health Organization
   C. It is a highly sensitive test for the diagnosis of TB, including MDR TB, with markedly decreased time to diagnosis compared to liquid or broth culture
   D. It can rapidly identify TB strains resistant to all first line TB drugs

10. In the past 5 years, there has been tremendous progress in expanding the pipeline of new drugs active against TB, including MDR TB. What are the names of two such drugs?
   A. Pyrazinamide and cycloserine
   B. Kanamycin and para–aminosalicylic acid
   C. Clarithromycin and linezolid
   D. Bedaquiline and delamanid

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	6. A B C D	**7.** A B C D	**8.** A B C D	**9.** A B C D	**10.** A B C D

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Please note: CE credit letters and long-term credit retention information will only be issued upon receipt of completed evaluation form.

PROGRAM OBJECTIVES: Having completed this activity, are you better able to:

		Strongly Agree				Strongly Disagree
Objective 1:	Describe the tools used to diagnose TB disease and LTBI.	5	4	3	2	1
Objective 2:	Summarize the treatment options for LTBI.	5	4	3	2	1
Objective 3:	Summarize the new tools for diagnosing and new drugs for treating MDR and XDR TB	5	4	3	2	1

OVERALL EVALUATION:	Strongly Agree				Strongly Disagree
The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
The information presented will influence how I practice.	5	4	3	2	1
The information presented will help me improve patient care.	5	4	3	2	1
The author demonstrated current knowledge of the subject.	5	4	3	2	1
The program was educationally sound and scientifically balanced.	5	4	3	2	1
The program avoided commercial bias or influence.	5	4	3	2	1
The self-assessment was appropriate and helpful.	5	4	3	2	1
Overall, the program met my expectations.	5	4	3	2	1
I would recommend this program to my colleagues.	5	4	3	2	1

Based on the content of the activity, what will you do differently in the care of your patients? (check one)

- ☐ Implement a change in my practice.
- ☐ Seek additional information on this topic.
- ☐ Do nothing differently. Current practice reflects activity recommendations.
- ☐ Do nothing differently as the content was not convincing.
- ☐ Do nothing differently. System barriers prevent change.
- ☐ Not applicable. I do not see patients in my current position.

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide us with a brief description of how you plan to do so.

_____

May we contact you in two months to see how you are progressing on the changes indicated above?

☐ Yes. Please provide your email address. _____

☐ No. I do not wish to participate participate in the follow-up assessment.

If you are not able to effectively implement what you learned at this activity, please tell us what the system barriers are (e.g., reimbursement issues, managed care rules, formulary decisions, countervailing practice guidelines, etc).

_____

Please list any topics that you would like addressed in future educational activities.

_____

Medical Monitoring Project

continued from page 1

There are two components to the study in New Jersey:

1. **Provider component:** The NJDOH identified a representative sampling of HIV medical care facilities in the state. NJDOH approached the 25 providers selected for this cycle in March 2013. Each facility was mailed information about the MMP as well as details about their role in the project.
2. **Patient interviews.** In addition, a random sample of about 400 patients (total) from the selected facilities is drawn. The selected patients have the opportunity to complete an interview, in return they are given a $40.00 Visa gift card. The interview data is supplemented with information from participants' medical records.

The MMP takes measures to ensure that the project is not burdensome to providers or participating patients; patient interviews and record reviews are completed by the NJDOH staff working on the MMP. All data is collected and treated in a confidential manner: no names are ever directly shared with the CDC or other collaborating agencies. Since the MMP is considered enhanced disease surveillance, it is covered by the Health Insurance Portability and Accountability Act (HIPPA) Privacy Rule [45CFR 164.512(b)]. The HIPPA language states that "…covered entities may disclose without individual authorization, protected health information to public health authorities authorized by law to collect or receive such information for the purpose of preventing or controlling disease…" The NJDOH is acting within its capacity as a public health authority, its goal is to better delineate issues and trends among the HIV population.

Further information about the MMP

National MMP:

http://www.cdc.gov/hiv/topics/treatment/MMP/index.htm

MMP in New Jersey:

Barbara Bolden, PhD, MMP Principal Investigator, (609) 984-5940 and *bbolden@doh.state.nj.us*

Provider Advisory Board

MMP has a national Provider Advisory Board (PAB) consisting of an HIV care provider from each project area. The PAB representative need not be from a selected facility. The PAB was developed to foster collaboration between local and national MMP staff and HIV care providers and advise local and national MMP staff on aspects related to the development and implementation of the MMP. They also serve as local peer resources for those HIV care providers approached to participate in this enhanced surveillance initiative.

Maximum participation by providers and patients will increase the likelihood of obtaining information that is truly representative of patients in care for HIV. The success of the MMP depends on the providers and patients selected to participate. ❖

[1] CDC. July 2012. HIV in the United States: At A Glance. Available at: *http://www.cdc.gov/hiv/resources/factsheets/PDF/HIV at a glance.pdf*

Maximum participation by providers and patients will increase the likelihood of obtaining information that is truly representative of patients in care for HIV.

HIV: Update on Progress Towards a Cure and Vaccine

Aria Williams, DO

Scientific advances over the past three or four years have renewed optimism in the search for a cure for HIV. Optimism entered the public spotlight with the "cure" of Timothy Brown, the man better known as "the Berlin patient".

Incidental cure of HIV with stem cell transplant

Timothy Brown, an American, was diagnosed with HIV in 1995. In 2006, while living in Germany, he also developed leukemia. His physician, Gero Hutter, treated Brown using total body irradiation and two blood stem cell transplants (a year apart) using a donor with a rare gene mutation (CCR5-Δ32 mutation in both genomic copies of a gene encoding a cell-surface chemokine receptor called CCR5) that confers resistance to HIV.

Sterilizing cure versus functional cure

- **Sterilizing cure:** Sterilizing cure refers to complete elimination of all HIV-infected cells from HIV infected individuals and an HIV RNA viral load of less than 1copy per ml.
- **Functional cure:** The functional model for HIV cure resembles the cancer model of cure, in that the disease is placed into a state of drug-free remission. HIV-infected individuals maintain long term health in the absence of treatment with extremely low levels of viremia, less than 50 copies per.[1]

Brown was heterozygous for CCR5-Δ32. Following the transplant procedures, his CD4 cells circulating in the blood were homozygous for CCR5-Δ32. After 600 days without antiretroviral therapy (ART), his blood, bone marrow and bowel HIV levels were below the limit of detection; the virus was thought to be present in other tissues. However, biopsies of the brain, intestines, liver, lymph nodes, bone marrow were all negative for virus. His antibody titers are declining just as expected had he been vaccinated against HIV: antibody response was strong at first, but later weakened. It is speculated that the weakening of the antibody response is due to the lack of re-exposure. It is predicted that, in a couple of years, his HIV antibody test will be negative.[2,3,4]

Subsequent presentations of possible HIV cure

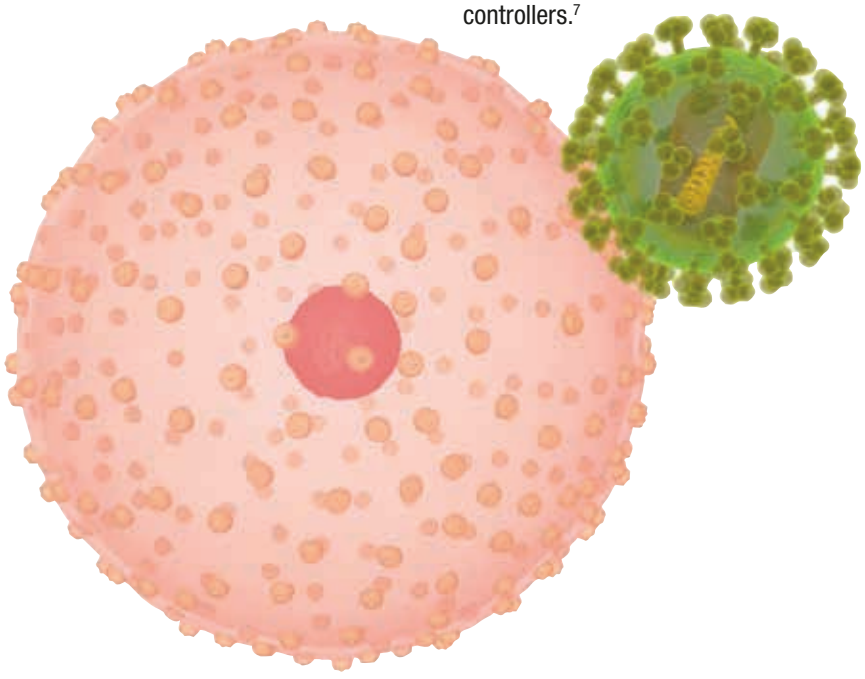
At AIDS 2012, an oral abstract was presented about two men with HIV and lymphoma who underwent stem cell transplants in Boston. One was infected with HIV perinatally, the other through sexual contact, and they had been on ART for 3–4 years at the time of transplant. Both patients were CCR5-Δ32 heterozygous, meaning they carried a single copy of the mutation (not 2 copies, like Brown's donor) so their cells were only partially resistant to HIV; the donors did **not** have naturally resistant cells. The men had HIV RNA suppressed on ART before their transplants, but still had residual HIV DNA in CD4 T-cells and possibly other reservoirs.

Both men did receive chemotherapy prior to their transplants but unlike Timothy Brown, they did not undergo whole body radiation and remained on ART. Eight months after the transplants, HIV DNA in peripheral blood mononuclear cells (HIV reservoir cells) became undetectable.[5] After 2 years of follow-up for one patient and 3.5 years for the other, both men have remained undetectable for replicating virus and viremia using a single copy assay.[4] Like Brown, the two men also showed decreases in HIV-specific antibodies, suggesting there is not enough remaining virus to trigger an immune response.

Though these 2 patients and Timothy Brown offer us the possibility of a functional cure, maybe even a sterilizing cure, due to the cost and high mortality (20–30%) associated with stem cell transplant, this procedure does not meet the criteria for a scalable cure.[6]

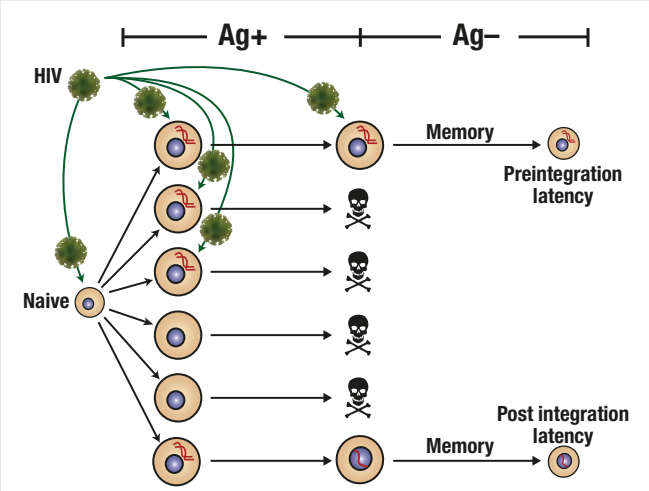
Early treatment as a "cure"

A second oral abstract at AIDS 2012, ANRS VISCONTI study, gives preliminary evidence for a functional cure. Twelve French patients were initiated on ART within 10 weeks of acute HIV infection. After about 3 years, medications were discontinued.[7] About seven years after cessation of ART, these patients have maintained long-term control of their HIV, with viral loads less than 1.7 log copies per ml. Researchers used elite controllers, (who have the ability to suppress plasma viremia without ART), as the control group. They found that study patients, after treatment interruption, had a low but inducible HIV reservoir that was similar to that of elite controllers.[7]



Most recently in the news is the case of a 2½ year old toddler from Mississippi, reported to be functionally cured of HIV. The mother initially presented to the hospital in labor without any prior prenatal care. The mother tested positive for HIV infection.[8] The standard ARV prophylaxis for infants born to HIV-infected women, who have not received antepartum ART, is zidovudine for 6 weeks combined with three doses of nevirapine in the first week of life.[9] However the infant was immediately started on a three-drug ART regimen. Two HIV RNA tests resulted in detectable plasma viral loads, confirming infection. After 29 days the infant's plasma viral load was undetectable. At 18 months the toddler fell out of care for five months and was not receiving ART. Upon return to care, viral loads were checked and found to be undetectable. Researchers, using ultrasensitive assays found tiny amounts of plasma viral RNA. However, they found no virus able to replicate or cellular reservoirs in the body.[10] This case offers another example of the "proof of concept" in terms of HIV cure. This case, if it can be replicated through clinical trials, may change the way we treat pediatric patients born to HIV-infected mothers.

Figure 1: T cell antigen-based activation and mechanisms for establishing of pre-integration and post-integration latency



Source: Buenz, E. and Badley, A. Impact of mitochondrial regulation of apoptosis on the pathogenesis and treatment of HIV-1-induced immunodeficiency. *Mitochondrion.* 2004;(4):235–254. Available at http://www.sciencedirect.com/science/article/pii/S1567724904000996

If it can be replicated through clinical trials, the case of the 2½ year old toddler from Mississippi may change the way we treat pediatric patients born to HIV-infected mothers.

Obstacles to cure

Viral persistence: HIV viral persistence in viral reservoirs is an important hurdle in finding a cure for HIV. HIV viral persistence is defined as low levels of viremia despite being on appropriate ART. A viral reservoir is a cell type or site within the body in which some form of the virus accumulates and persists with greater stability than does the main pool of actively replicating virus, even while on ART. Several studies using an ultrasensitive assay (detecting 1 copy per ml), were able to demonstrate low levels of viremia around 3–5 copies per ml in 80% of patients.[1] It is this reservoir of virus that seeds a viral rebound.[11]

Multiple mechanisms have been cited that likely play a role in HIV viral persistence. These include

- **CD4 T-cell latency:** CD4 T-cells are the major reservoir for cells that harbor post-integration latency see Figure 1. These cells consist of "resting" memory CD4 T-cells (transcriptionally inactive), that can remain for decades once integration of viral DNA has occurred. Because ART primarily targets replicating cells, they are unaffected by these medications and are also able to evade the host immune recognition.[1] This creates a stable reservoir on ART, in which the virus is intermittently released. Though the majority of these cells are "resting" CD4 T-lymphocytes, there may also be macrophages, astrocytes, thymocytes and possibly hematopoietic progenitor cells.[7, 11]
- **Ongoing viral replication:** It has been speculated that persistent viremia might be explained by ongoing replication in activated CD4 cells while on ART. One test of ongoing viral replication is to intensify ART regimens to determine whether viral load can be reduced beyond what is achieved with standard suppressive regimens. Several trials tried this, but in each case without success. These findings were interpreted to indicate a lack of ongoing viral replication, and the maintenance of reservoirs of virus in long-lived cells. Ongoing replication might also be evidenced by genetic evolution. Because HIV is known to generate mutations with each round of replication, studies have compared the genomes of pre-therapy virus with those present in plasma after years of therapy. In each case, there is little evidence of divergence during therapy.[12] These findings suggest a lack of ongoing viral replication and maintenance of virus in a reservoir of latently infected cells (that are not susceptible to ART or host immune responses).
- **Anatomical reservoirs:** Another area of interest is anatomical compartments where HIV reservoirs can be found, such as, in the gastrointestinal tract, genital tract, and the brain.[11] These sites may represent distinct biological compartments that may have unique barriers to standard treatments. At these sites the virus can persist as active replicating cells or latently infected cells.[1]

HIV associated immune dysfunction: HIV associated immune dysfunction in patients on ART has also been suggested to play a role in viral persistence. Multiple mechanisms that are poorly defined may contribute to this, such as, lymphoid tissue fibrosis, loss of gut mucosal integrity, an excessive burden of co-infections, and a loss of immunoregulatory cells. In addition, inflammation and immune cell activation may in turn increase the number of T-cells susceptible to infection, increase proliferation of latent virus, alter T-cell survival and function (i.e. apoptosis) and decrease the ability of host immune response to recognize and kill the HIV virus.[11]

Strategies for Cure

Current literature suggests the following strategies for an HIV cure:

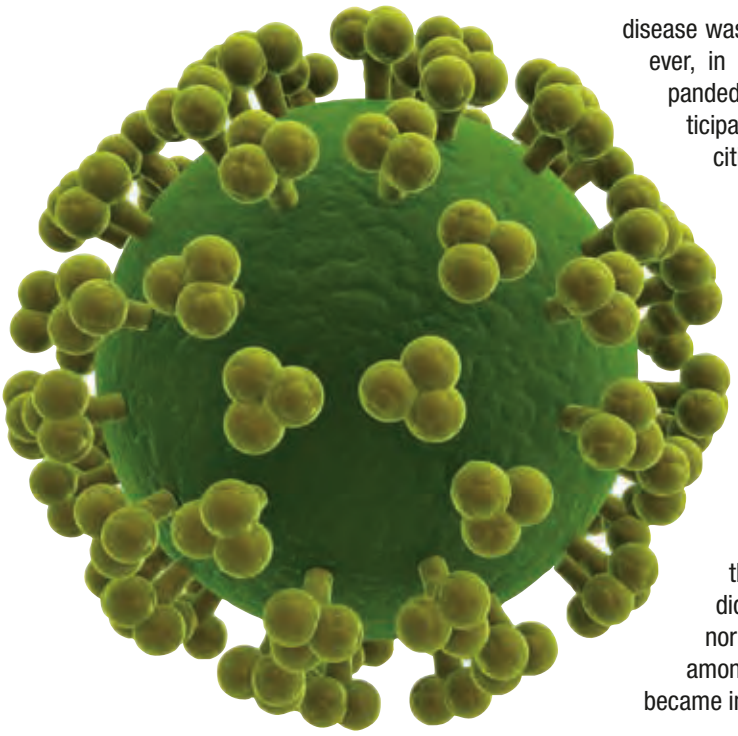
- **Treatment intensification:** Several studies have now demonstrated that treatment intensification (such as the addition of agents, such as enfuvirtide, additional protease inhibitors or raltegravir, to an already suppressive regimen) appears to have little impact on latent reservoirs. Some potential and promising approaches that may reduce the latent reservoir include very early initiation of ART and the use of agents that could potentially reverse latent infection.[1]
- **Early treatment:** Other studies have looked at early treatment with ART during acute infection. This has been suggested as a possible strategy that can be used to limit seeding of the HIV reservoir and preserve the immune response. The recent ANRS VISCONTI trial (see page 17) showed that patients given early treatment were able to control infection after cessation of therapy and had a low level of reservoir cells. Some expert clinicians believe that a combination of both may be needed to decrease viremia, decrease latently infected cells, and preserve immune function.[13]
- **Eradication of the virus from latent HIV-infected cells:** Activating virus production in latent cells causes viral cytopathic effects that result in cell death. Multiple molecules are being studied as inducers of HIV latent cells, for example, cytokines and other molecules such as, histone deacetylase inhibitors (HDACi), prostatin, microRNAs,[14] methylation inhibitors and valproic acid.
  - IL-7 is a cytokine that has been shown to induce activation of latently infected T-cells.[1] The ERAMUNE-01 Trial is currently underway using IL-7 and ART intensification with raltegravir and maraviroc. The primary end point of this study is the decrease from baseline in HIV DNA in the peripheral blood mononuclear cells (reduction of the viral reservoir).[15]
  - HDACi are drugs that can modify gene expression by changing the acetylation state of genes. These drugs are also able to turn HIV genes on in latently infected cells in vitro. In cancer cells, HDACi induce cell death of the malignant cells and many HDACi are now in advanced clinical development for the treatment of different cancers. Vorinostat (also called SAHA), is already licensed for the treatment of cutaneous T cell lymphoma, is well tolerated in humans, and has significant activity in promoting HIV or turning HIV genes on in vitro.[1]
- **Making the cells resistant to infection:** Gene therapy is a strategy currently under consideration to make CD4 cells resistant to infection. This strategy is somewhat similar to that undergone by the Berlin patient, in that the patient was given a hematopoietic stem cell transplant from a donor who was homozygous for the CCR5 co-receptor mutation, ultimately making his cells resistant to HIV infection. This homozygosity for this co-receptor mutation has also been documented in a group of individuals who were frequently exposed to HIV but are resistant to infection with the virus. What gene therapy attempts to do is to imitate this expression of this genotype using the patient's own cells. Gene transfer and modification tools are currently being studied. For example, the use of RNA interference to decrease CCR5 expression and zinc finger nucleases to permanently disrupt the CCR5 open-reading frame causing a gene knockout. Success has been seen with mice models via introduction zinc finger nuclease. Preclinical studies have demonstrated the ability to suppress HIV-1 in vivo, when used to modify human T cells or hematopoietic stem cells in mice models.[16]

Vaccines

An update on progress towards a cure for HIV would be incomplete without at least a superficial summary of recent findings from HIV vaccine research. Since the 1980s, multiple experimental preventive vaccines have been studied in nonhuman primates. Of those studied in nonhuman primates, only five vaccines have been tested for efficacy on human volunteers. Of these five vaccines, only the phase three placebo-controlled RV144 trials, a prime-boost HIV vaccine, was found to be safe, well tolerated, and suitable for large-scale further research. Three other vaccine trials failed to show efficacy in prevention of HIV and one, the HVTN 505, was recently discontinued.[17]

The RV144 trial was a randomized, intention to treat trial of 16,402 patients in Thailand. The trial tested the safety and efficacy of a prime-boost regimen of vaccines. The primer

Since the 1980s, multiple experimental preventive vaccines have been studied in nonhuman primates. Of those studied in nonhuman primates, only five vaccines have been tested for efficacy on human volunteers. Of these five vaccines, only the phase three placebo-controlled RV144 trials, a prime-boost HIV vaccine, was found to be safe, well tolerated, and suitable for large-scale further research.



dose consisted of the ALVAC-HIV vaccine and booster dose consisted of the AIDSVAX B/E vaccine, a glycoprotein 120 vaccine. After 42 months of follow up, 125 of the 16,402 participants contracted HIV through behavior unrelated to their study participation. Of those 125, 74 infected persons had received placebo and 51 had received the vaccine. It is statistically significant that the group that received the vaccine has an infection rate 31.2% lower than the group who received placebo.[18]

The Phase IIb study **HVTN 505**, was started in 2009 and discontinued by the National Institute of Allergy and Infectious Diseases (NIAID) in late April 2013. The HVTN 505 used a DNA/recombinant (r) Ad5 prime-boost combination. The initial goal of this study was to determine whether the vaccine decreased the amount of virus in the blood of recipients who later became infected with HIV; prevention of disease was a secondary goal. However, in 2011 the study was expanded from 1350 to 2,500 participants (at 21 sites in 19 U.S. cities) to determine whether the vaccine regimen was at least 50% effective at preventing HIV infection 18 months after immunization. The HVTN 505 trial was discontinued because an independent data and safety monitoring board (DSMB) found during a scheduled interim review that the vaccine regimen did not prevent HIV infection nor did it reduce viral load among vaccine recipients who became infected with HIV.[19]

Vaccine as cure

Not only are vaccines being studied in terms of prevention but also to decrease viral reservoirs. EraMune 02 study for example, is using immunomodulation through a prime booster vaccine along with ART intensification to look at the effects on viral reservoir.[15] EraMune 02 is a nation-wide trial — with sites in Illinois, California and New York — that started in November 2009 and was scheduled to be completed in December 2012.

Pre-exposure prophylaxis

iPrEx: The iPrEx clinical trial examined the effectiveness of pre-exposure prophylaxis (PrEP) among men who have sex with men (MSM). Researchers found that daily oral use of tenofovir and emtricitibine provided an average of 44% additional protection to MSM who also received a comprehensive package of prevention services that included monthly HIV testing, condom provision, and management of other sexually transmitted infections. Among MSM with detectable levels of the medication in their blood, the risk of acquiring HIV was decreased by 90%.[20]

TDF2 and **Partners:** There are two other studies that examined PrEP in heterosexual adults, TDF2 and Partners. The TDF2 trial found that the use of once a day tenofovir and emtricitibine decreased the risk of HIV infection by 62%, prompting approval of ART for the purpose of PrEP. Partners PrEP evaluated once a day tenofovir or tenofovir and emtricitibine and found a decrease in acquiring the infection by 75% and 67%, respectively. Participants with detectable drug levels decreased their risk by 90% and 86% respectively.[20] Due to the compelling results of these studies, in July 2012, Center for Disease Control published the interim guidelines in the Morbidity and Mortality Weekly Report for the use of PrEP in MSM. This was followed, in August 2012, by the interim guidelines for the use of PrEP in heterosexually active adults.

VOICE: the Vaginal and Oral Interventions to Control the Epidemic (VOICE) was a Phase IIb HIV prevention trial that began in September 2009 and enrolled 5,029 women in Uganda, South Africa and Zimbabwe, with follow-up completed in August 2012. The trial tested whether specific ARVs were safe and effective in preventing sexual transmission of HIV in women. The study focused on two ARV-based approaches: daily oral PrEP (with either tenofovir or a combination of tenofovir and emtricitabine, marketed as Truvada) and daily use of a vaginal microbicide containing a tenofovir gel. Of the three products tested in VOICE none proved to be effective among the women enrolled in the trial. Although Truvada was found to be effective in other trials in other populations (see TDF2 and Partners, above), its poor performance in VOICE was due to poor adherence, which was low across all groups, particularly women who were under 25 years of age and single.

Although Truvada was found to be effective in other trials in other populations, its poor performance in VOICE was due to poor adherence, which was low across all groups, particularly women who were under 25 years of age and single.

Conclusion

Given the lack of impressive data coming out of years of HIV vaccine trials — only the RV144 trial showed a reduced risk of HIV infection, but only by 31% — attention has returned to the question of a cure for HIV. Over the past 30 years of HIV-related research, hopes for a cure have been tenuous. However, with the recent "proof of concept" provided by the cure of the Berlin patient after blood stem cell transplant and other advances in understanding the virus, there is now a renewed optimism.

The optimism was further fuelled by the ANRS VISCONTI study, which described the functional cure of 12 French patients through the use of early and aggressive ART. The report of the functionally cured toddler in Mississippi provided additional evidence that early aggressive treatment could potentially cure perinatally acquired HIV. Together these findings offer direction for research development. Will the fourth decade of HIV be the decade during which science will overcome the numerous obstacles to identifying an HIV vaccine and a discovering a cure for HIV? ❖

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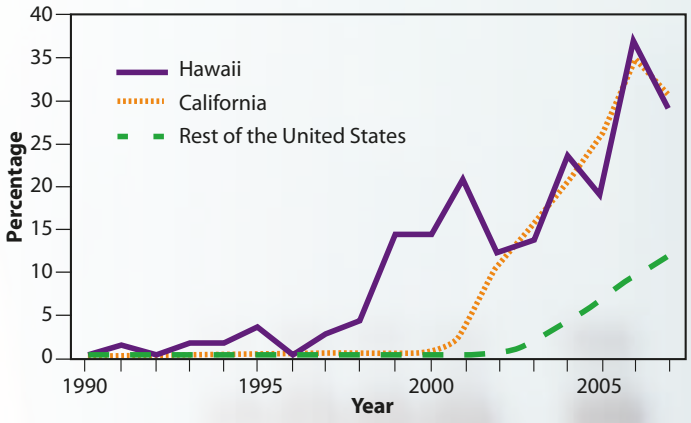
The Growing Threat of Multidrug-Resistant Gonorrhea

This article is from the CDC Grand Rounds article with the same title, reported by Edward W. Hook, III, MD; William Shafer, PhD; Carolyn Deal, PhD; Robert D. Kirkcaldy, MD; John Iskander, MD; and Robert D. Kirkcaldy. Original article available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6206a3.htm

With more than 300,000 cases reported in 2011, gonorrhea is the second most commonly reported notifiable infection in the United States. Infection with *N. gonorrhoeae* is spread through sexual contact and, depending on the anatomic site of exposure, can cause acute urethritis, cervicitis, proctitis, or pharyngitis. However, most cases of gonorrhea are asymptomatic, particularly cervical, pharyngeal, and rectal infections. Untreated or inadequately treated gonorrhea can facilitate human immunodeficiency virus (HIV) transmission and cause serious reproductive complications in women, such as pelvic inflammatory disease, ectopic pregnancy, and infertility. Other severe complications, including disseminated gonococcal infection and neonatal conjunctivitis and blindness, still occur in resource-limited settings, but are now rare in the United States.

Empiric antimicrobial therapy is used for treatment of gonorrhea. Antimicrobial susceptibility testing generally is not routinely available in clinical practice, and early diagnosis and effective antimicrobial treatment of patients and their partners has been the mainstay of gonorrhea control and prevention; thus, gonococcal antimicrobial resistance poses a grave challenge.

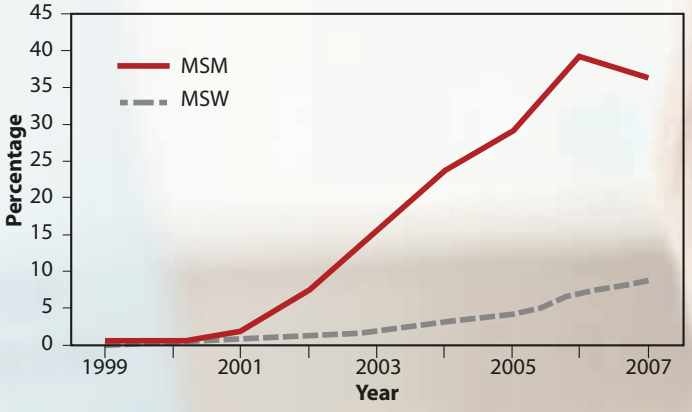
Figure 1: Prevalence of ciprofloxacin resistance* in urethral *N. gonorrhoeae* isolates collected from men in the United States, by location — GISP, 1990–2007



** Defined as minimum inhibitory concentrations ≥1 µg/mL.*

Recognizing the need for ongoing surveillance of gonococcal antimicrobial resistance, CDC developed the Gonococcal Isolate Surveillance System (GISP) in 1986. GISP is a CDC-supported sentinel surveillance system that monitors gonococcal antimicrobial susceptibility among urethral *N. gonorrhoeae* isolates collected from men attending participating sexually transmitted disease (STD) clinics. The objectives are to provide a scientific basis for gonorrhea treatment recommendations and to allow changes in treatment recommendations before widespread treatment failures become a major public health problem.

Figure 2: Prevalence of ciprofloxacin resistance* in urethral *N. gonorrhoeae* isolates collected from men in the U.S., by gender of sex partner — GISP, 1999–2007



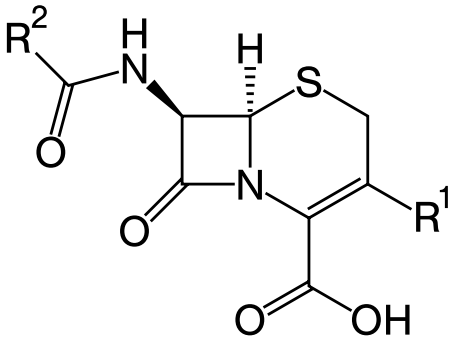
Abbreviations: MSM = men who have sex with men; MSW = men who have sex exclusively with women.
** Defined as minimum inhibitory concentrations ≥1 µg/mL.*

Fluoroquinolone-resistance: GISP monitored emerging fluoroquinolone-resistant *N. gonorrhoeae* (QRNG) in the United States during the 1990s and 2000s. During this period, fluoroquinolones were widely used for treatment of gonorrhea because they were safe, effective, inexpensive, and available in oral forms. Gonococcal fluoroquinolone resistance had emerged in East Asia during the 1990s and was observed sporadically in the United States by GISP. In the early 2000s, QRNG emerged in the United States, spreading initially in Hawaii and California (Figure 1). Men who have sex with men (MSM) were and remain disproportionately affected by QRNG (Figure 2). By 2007, the prevalence of QRNG was >5% among GISP isolates collected throughout the United States, prompting CDC to no longer recommend the use of fluoroquinolones for gonorrhea treatment. Spectinomycin, an alternative treatment, had not been available in the United States since 2006, so cephalosporins (such as cefixime and ceftriaxone) were the only remaining antimicrobials recommended for treatment of gonococcal infections.

Cephalosporins remained the foundation of gonorrhea treatment in the 2010 CDC STD treatment guidelines. These updated guidelines increased the recommended dosage of ceftriaxone to 250 mg and included broadened recommendations for combination therapy: a cephalosporin, preferably ceftriaxone 250 mg as a single intramuscular dose, should be administered with a second antimicrobial. Combination therapy treats frequently co-occurring pathogens (e.g., Chlamydia trachomatis) and might hinder the spread of cephalosporin antimicrobial resistance.

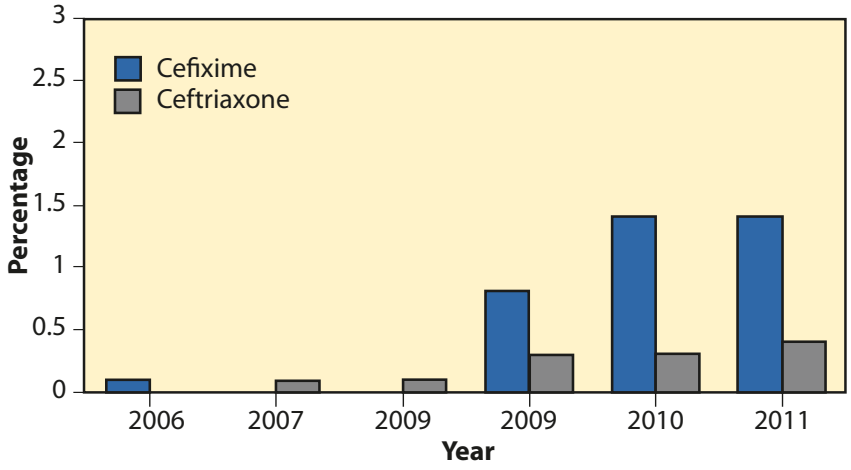
The Growing Threat of Multidrug-Resistant Gonnorrhea

This Gram-stained photomicrograph reveals the presence of intracellular Gram-negative, Neisseria gonorrhoeae diplococcal bacteria, amongst numerous white blood cells (WBCs) known as polymorphonuclear leukocytes, or PMNs. CDC/ Bill Schwartz



Cephalosporin resistance: Unsuccessful treatment of gonorrhea with oral cephalosporins, such as cefixime, was identified in East Asia, beginning in the early 2000s, and in Europe within the past few years. GISP now provides growing evidence that cephalosporin resistance might be emerging in the United States. Cefixime minimum inhibitory concentrations (MICs) recently increased, suggesting that the effectiveness of cefixime might be threatened. The percentage of isolates with elevated cefixime MICs (≥0.25 µg/mL) increased from 0.1% in 2006 to 1.4% in 2011 (Figure 3). The increases were most pronounced in isolates collected from men in the western United States and from MSM, the region and population in which QRNG first emerged.

Figure 3: Percentage of urethral *N. gonorrhoeae* isolates with elevated cefixime minimum inhibitory concentrations (MICs) and elevated ceftriaxone MICs* — GISP, 2006–2011†



* *Elevated cefixime MICs defined as ≥0.25 µg/mL; elevated ceftriaxone MICs defined as ≥0.125 µg/mL.*

† *Isolates not tested for cefixime susceptibility in 2007 and 2008.*

The development and spread of cephalosporin resistance in *N. gonorrhoeae*, particularly ceftriaxone resistance, would greatly complicate treatment of gonorrhea. Previously recommended antimicrobials likely cannot again be routinely prescribed for empiric gonorrhea treatment. *N. gonorrhoeae* maintains previously acquired antimicrobial resistance phenotypes, even if the antimicrobial is no longer used for treatment. In 2011, 11.8% of isolates in GISP were penicillin-resistant, 22.7% were tetracycline-resistant, and 13.3% were fluoroquinolone-resistant. Unlike resistance mutations in many other bacteria, resistance

mutations in *N. gonorrhoeae* might actually improve the survival of resistant strains, even in the absence of antimicrobials.

Challenges in detecting and responding to the emergence of multidrug-resistant gonorrhea also exist. Rapid detection of resistant infections is facilitated by local antimicrobial susceptibility testing, which at this time requires live organisms isolated by culture. However, as the use of nucleic acid amplification tests (NAATs) has expanded, the number of *N. gonorrhoeae* cultures performed by public health laboratories has decreased rapidly, and the capacity of U.S. laboratories to perform culture for *N. gonorrhoeae* has declined. In addition, many local and state STD programs have experienced reductions in funding and infrastructure in recent years, which might hamper the ability of these programs to detect resistant infections and ensure that patients and partners are treated effectively.

What public health agencies and partners can do

Several steps taken now might delay the emergence of cephalosporin-resistant strains, mitigate the public health consequences of expanded resistance, and prevent a return to the era of untreatable gonorrhea. Clinicians can help prevent sequelae and spread of gonorrhea by:

- Eliciting sexual histories from their patients, screening sexually active MSM and high-risk sexually active women for gonorrhea at least annually at exposed anatomic sites, and treating appropriately.
- Counseling sexually active adults, particularly those living in high prevalence areas, to engage in mutually monogamous partnerships with uninfected partners and to consistently and correctly use latex condoms, which can reduce transmission.
- Strengthening surveillance by maintaining vigilance for treatment failures, collecting isolates for susceptibility testing from such patients, and promptly notifying the local public health STD program.

Local public health laboratories can contribute by maintaining or rebuilding capacity to perform culture for *N. gonorrhoeae* or partnering with laboratories that can. Laboratories that conduct gonococcal antimicrobial susceptibility testing are requested to promptly notify the ordering clinician and local STD control program of isolates with elevated cephalosporin MICs (cefixime MIC ≥0.25 µg/mL or ceftriaxone MIC ≥0.125 µg/mL).

GISP now provides growing evidence that cephalosporin resistance might be emerging in the United States.

Current gonorrhea treatment recommendations

Gonorrhea at any anatomic site should be treated with:

- Ceftriaxone as a single 250 mg intramuscular dose
  PLUS
- Azithromycin 1g as a single oral dose
  OR
- Doxycycline 100 mg, orally, twice daily for 7 days

If this recommended regimen cannot be used, alternative treatment options for urogenital or rectal gonorrhea:

1. **If ceftriaxone is not available:**
   Cefixime 400 mg as a single oral dose
   PLUS
   Azithromycin 1 g as a single oral dose
   OR
   Doxycycline 100 mg, orally, twice daily for 7 days
2. **If the patient has severe cephalosporin allergy:**
   Azithromycin 2 g as a single oral dose.

If either of these two alternative regimens is prescribed, the patient should return in 1 week for a test of cure.

Within several years, molecular assays for detecting genetic mutations associated with resistance might be available and could enhance surveillance and clinical management. However, molecular assays will not supplant culture-based antimicrobial susceptibility testing for surveillance, which still will be needed to detect novel resistance phenotypes and genotypes. Although a gonococcal vaccine remains an elusive goal, efforts to develop a vaccine are continuing.

Based on past and current data, *N. gonorrhoeae* will continue to acquire antimicrobial resistance. However, experience and current data suggest that public health actions outlined in this report provide the best chance of averting the unfavorable outcome of multidrug-resistant gonorrhea, greater disease burden, heightened risk for sequelae, and greater health-care costs. ❖

Adapted from: CDC Grand Rounds. "The Growing Threat of Multidrug-Resistant Gonorrhea." MMWR. February 15, 2013 / 62(06);103-106. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6206a3.htm

Reshaping Primary Care through Patient-Centered Medical Homes

Andrea Norberg, Executive Director and Denise Anderson-Carr, Program Manager, HIV Medical Homes Resource Center
François-Xavier Bagnoud Center, School of Nursing, University of Medicine and Dentistry of New Jersey

Pictured from left to right: Macsu Hill, Andrea Norberg and Denise Carr-Anderson

The passage of the Patient Protection and Affordable Care Act (ACA) of 2010 helped reshape primary care by funding the development of care approaches that better integrate and coordinate services, such as the patient-centered medical home (PCMH). Primary care practices that adopt this model offer the comprehensive, patient-centered care that is especially needed by those who are chronically ill, including those with HIV.[1]

The PCMH (sometimes referred to as the advanced primary care or the healthcare home) is a promising model for transforming the organization and delivery of primary care. The concept was originally introduced in 1967 by the American Academy of Pediatrics (AAP) — initially referring to a central location for archiving children's medical records — to coordinate comprehensive care for children with special health needs. In March 2007, the AAP, American Academy of Family Physicians, American College of Physicians, and the American Osteopathic Association developed the joint principles to describe the characteristics of the PCMH. Since then, PCMH has become the model of care supported by the ACA.[2]

HIV MHRC
HIV Medical Homes Resource Center

The PCMH provides comprehensive care and assumes accountability for managing a patient's physical and mental healthcare needs, including prevention, wellness, acute and chronic care. It does this though a team-based approach. The PCMH coordinates care across all elements of the broader healthcare system, including specialty care, hospitals, home health care, and community services and supports.

PCMH defined

The PCMH provides comprehensive care and assumes accountability for managing a patient's physical and mental healthcare needs, including prevention, wellness, acute and chronic care. It does this though a team-based approach. The team often includes physicians, advanced practice nurses, physician assistants, nurses, pharmacists, nutritionists, social workers, educators, and care coordinators.

As the name implies, the PCMH is a patient-centered approach, i.e., an approach that is underpinned by a partnership with patients and their families and strives to address the whole person (unique needs, culture, values, and preferences). The PCMH coordinates care across all elements of the broader healthcare system, including specialty care,

hospitals, home health care, and community services and supports. Effective communication occurs with the patient, their family and the rest of the health system at each juncture. Access to care is enhanced through shorter waiting times for urgent needs, in-person hours, around-the-clock telephone or electronic access to a member of the care team, and alternative methods of communication such as email and telephone care. Lastly, the PCMH is committed to quality and safety. A PCMH uses evidence-based medicine and clinical decision support tools to guide shared decision making with patients and families, engages in performance measurement and improvement, measures and responds to patient experiences and patient satisfaction, and practices population health management.

Intersection of the PCMH and Ryan White HIV programs

Since enacted in 1990, the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act has evolved through successive legislative actions to meet changing HIV prevention, care and treatment needs in conjunction with shifts in the scope and demographics of the HIV epidemic. Most recently, the Ryan White Treatment Extension Act of 2009 incorporated a strong focus on the early identification of individuals with HIV to reduce the number of people who are unaware of their HIV infection. It also emphasizes the need to link and retain all HIV-positive individuals with ongoing care and services.

Historically, grantees providing health care through Ryan White funding have incorporated many of the principles of a PCMH, such as comprehensive, patient-centered care, evidence-based care and quality management. In 2009, Dr. Michael Saag said it best "The [Ryan White CARE] Act … unintentionally, created medical homes that are the best examples of how all of us should receive primary care."[3] Other aspects of becoming a PCMH may be more challenging to Ryan White agencies such as enhanced access. Addressing the range of service delivery issues involved in becoming a PCMH will position Ryan White grantees to work toward certification as a PCMH and for enhanced reimbursement.

HIV Medical Homes Resource Center

In November of 2011, The Francois-Xavier Bagnoud Center of the School of Nursing at the University of Medicine and Dentistry of New Jersey was awarded a cooperative agreement from the Health Resources and Services Administration HIV/AIDS Bureau to develop a national training and technical assistance resource center to assist Ryan White HIV Program grantees in understanding, developing and successfully applying to become recognized PCMHs. They partnered with the University of San Francisco, Department of Family and Community Medicine, Center for Excellence in Primary Care to form the HIV Medical Homes Resource Center (HIV-MHRC). Co-Principal Investigators are Carolyn Burr, EdD, RN and Andrea Norberg, MS, RN.

Ryan White grantees' response to the HIV-MHRC

In February and March 2012, the HIV-MHRC conducted an online needs assessment of Ryan White clinics to learn about their current progress and needs with respect to PCMH development and to inform development of HIV-MHRC activities and resources. Twenty-three percent of the 223 responding clinics had received certification as a PCMH (36 sites) or had a pending application (28 sites), representing a total of 51 clinics/practices in 20 states. PCMH certification is offered by a number of organizations, but the majority of clinics (61%) identified the National Committee for Quality Assurance recognition. Some clinics had been certified by more than one group.

Almost all responding clinics were interested in obtaining or maintaining PCMH certification, two-thirds (66%) were very interested and only 6 sites were not at all interested. Reasons for interest in PCMH certification included improving the quality and outcomes of patient care, advancing change in the practice and delivery of healthcare services, and incentive payments and reimbursements. About one-half of clinics without PCMH certification or a pending application reported that they had begun to work on the PCMH or had plans to begin work on an application within the next 6 to 18 months. However, respondents also identified barriers to PCMH development and certification that centered on needs for information, practice change and support and issues such as time, staffing and cost. When asked about training and technical assistance needs, they identified general topics related to PCMH development as well as those related to certification—including certification options, documentation requirements, and costs.

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To learn more about PCMHs and the HIV-MHRC, visit http://www.careacttarget.org//library/hiv-medical-homes-resource-center-hiv-mhrc. ❖

1. Henderson S, Princell CO, Martin SD. "The patient-centered medical home: this primary care model offers RNs new practice—and reimbursement—opportunities." *Am J Nurs.* 2012 Dec;112(12):54-9.
2. Patient-Centered Primary Care Collaborative. *Joint Principles of the Patient-Centered Medical Home.* February 2007. Accessed February 11, 2013 at: http://www.pcpcc.net/joint-principles
3. Saag, MS. "Ryan White: An Unintentional Home Builder". *AIDS Reader.* 19:166-168, April 24, 2009. Accessed February 11, 2013 at: http://www.theaidsreader.com/display/article/1145619/1408105

Increasing Pap Screening Rates

Jane Caruso, M.S.

Research has shown that HIV-positive women are about four times more likely than HIV-negative women to develop genital lesions and cervical cancer, with 20–60% of HIV-positive women showing signs of pre-cervical cancer.[1] "When compared with HIV-negative women, HIV-positive women with invasive cervical cancer present at more advanced stages and with cancer metastasizing to unusual locations. HIV-positive women have poorer responses to standard therapy and have higher recurrences and death rates, as well as shorter intervals to recurrence or death."[2]

Given the importance of cervical cancer screening to women with HIV, The New Jersey Cross Part Collaborative (CPC), which engages all Ryan White-funded medical providers in the state, has targeted the Pap screening measures for routine measurement and improvement activity. The measures are set by the Health Resources and Services Administration, HIV/AIDS Bureau (HAB) to support the implementation of quality management activities within Ryan White agencies.

The current CPC Pap smear target is 60%. In other words, providers in the CPC aim to obtain Pap smears according to national recommendations (see box below) from at least 60% of their Ryan White-funded female clients by June 2013.[3] Although Pap screening is a priority for the CPC, current rates are more than 20% shy of target, and increases over the past year have been negligible (see graph).[4] Many providers struggle to identify either a root cause for the low screening rates, or a feasible strategy to implement via Plan-Do-Study-Act (PDSA) cycles.

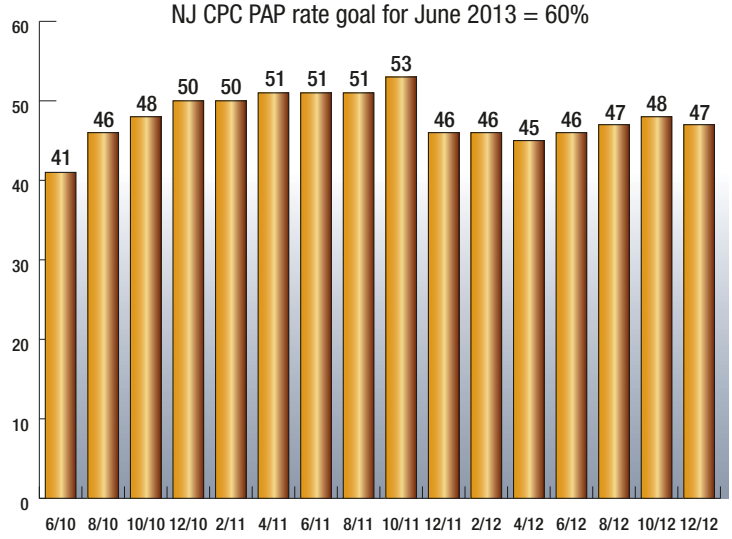
Agency for Health Care Policy and Research Recommendation on Pap smear for women with HIV

Obtain Pap smears from women with HIV twice during the first year after diagnosis of HIV infection; the Pap smears can be conducted six months apart. If both of these test results are normal, then testing can be modified to once a year.[5]

If testing shows ASC-H (atypical squamous cells—cannot rule out high-grade squamous intraepithelial lesion), LSIL (low-grade squamous intraepithelial lesion), or HSIL (high-grade squamous intraepithelial lesion), then some experts suggest that a colposcopy should be performed.[6]

To help target quality improvement activities, the CPC conducted a survey of all New Jersey Ryan White medical care provider agencies, 34 of the 40 agencies participated. Of those surveyed 67% indicated that they were having problems implementing annual Pap smears for the target population. From the provider perspective, the following barriers were mentioned:

New Jersey CPC Pap rates, June 2010–December 2012



- Lack of patient compliance in keeping GYN appointments — this is, by far, the most important reason women are not receiving annual screens. Time and time again, multiple appointments are made and missed.
- Appointments at gynecology (or "GYN" for short) clinics are hard to get and the wait time tends to be long.
- Patients with mental health and substance abuse issues are particularly hard to engage in GYN care.
- Patients don't seem to understand the importance of Pap screening to their health.
- Many patients simply do not want the screen.
- There are logistical problems with trying to track successful GYN appointments made outside of Ryan White clinic/hospital setting.
- Insufficient time to conduct Pap smears in the HIV clinic, dearth of the required level of expertise to conduct the screen.

The barriers to routine GYN care look somewhat different from the patient perspective. The Ryan White Part D Network in New Jersey was provided with federal funding to survey women of child-bearing age on access to GYN care. The survey included all seven of seven Ryan White agencies, reaching women in all 21 New Jersey counties. Despite the fact that providers describe patients as lacking an understanding of the importance of Pap screens, 96% of the patient respondents (n=85) mentioned that their HIV provider discussed with them the importance of an annual pap screen. The most significant factors identified by the women include:

- The GYN provider must be nice/caring/empathetic/supportive/non-judgmental. Being treated by a provider of similar culture was also noted as a preference.
- The doctor should be easy to talk to and explain things so they are simple to understand.

Increasing Pap Screening Rates

- The doctor should be female, if possible.
- Did not want to learn about yet another health problem (i.e., fear of diagnosis).
- Did not want to undergo a Pap smear because of the discomfort of the procedure.
- Did not want to disclose/discuss their HIV status with yet another provider. They did not want to see a different provider every time they went for GYN care.
- Did not want the procedure because there were too many people/students in the exam room.
- Waiting room time was too long or they were busy and had other priorities.
- Transportation and child care challenges.

The overall sentiment expressed by patients was that they wanted a provider with whom they could have a positive and trusting relationship. The patient/provider relationship is critical to women with HIV when considering ongoing and routine GYN care.

Training Opportunities: For agencies interested in training their staff to provide Pap smears on-site during the HIV visit, the NY/NJ AIDS Education and Training Center (AETC) offers free hands-on training for pap screens (for more information, see next article and back cover of this issue of AIDSLine).

[1] The AIDS Beacon, 2010. *Studies Examine Relationship Between HIV And Cervical Cancer In Women*. Accessed January 30, 2013 at: http://www.aidsbeacon.com/news/2010/07/23/studies-examine-relationship-between-hiv-and-cervical-cancer-in-women-aids-2010/

[2] HRSA. 2008. *HAB HIV Core Clinical Performance Measures for Adult/Adolescent Clients: Group 2.* Available at: http://hab.hrsa.gov/deliverhivaidscare/files/habgrp2pms08.pdf

[3] HAB Pap screening measure denominator is defined as: the number of HIV-infected women 18 years of age and older + females younger than 18 years of age with a reported history of sexual activity during the measurement period. Patients who had a hysterectomy for non-dysplasia/non-malignant indications are excluded from the denominator.

[4] The New Jersey CPC collects Pap screen data on a bimonthly basis. Each bimonthly data submission covers a one-year measurement period; data are trended at the agency, consortia, and statewide level.

[5] CDC. *MMWR*, "USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus: A Summary". July 14, 1995 / 44(RR-8);1-34. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/00038328.htm

[6] Centers for Disease Control and Prevention. "Cervical Cancer Screening for Women Who Attend STD Clinics or Have a History of STDs". *Sexually Transmitted Diseases Treatment Guidelines, 2010.* http://www.cdc.gov/std/treatment/2010/cc-screening.htm Page last reviewed January 28, 2011. Viewed October 7, 2012.

Best Practice Highlight: Jersey City Medical Center

Jersey City Medical Center's Center for Comprehensive Care (CCC) provides Pap smears during HIV consultations (rather than through a collaborating GYN provider). The CCC is a large urban facility that manages medical care and case management support for over 1000 patients. The female population eligible for a Pap screen averages 350 women. The current Pap rate is a stellar 85%, far exceeding the statewide average for Pap screens. Clinic Director, Matthew Zysman, attributes their success to the provision of on-site Pap screens that take place during the HIV visit. Co-location of services reduces patient burden by reducing medical appointments. This means that patients also incur fewer co-pay costs and interact with fewer new providers.

Pictured above: Jersey City Medical Center

Having staff who are able and willing to obtain Pap smears is critical component of a successful Pap program, but just as crucial is patient buy-in. The CCC staff believes in patient education, and they find time during medical or medical case management visits to assure that the patient understands the importance of annual pap screens to their overall health. The patients at the CCC have trusting relationships with their HIV providers. Patient comfort level is higher with providers they already know and with whom they routinely interact.

Pictured above: Dr. Adriana Grigoriu (Medical Director) and Matthew Zysman (Administrative Director)

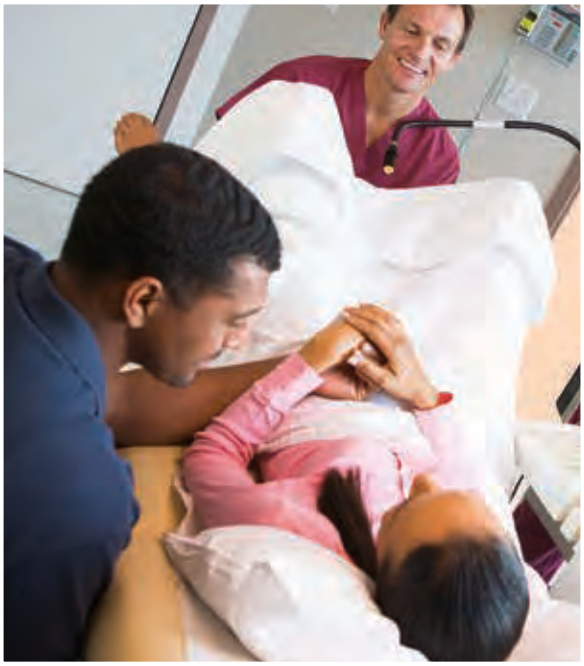
The CCC has four nurse practitioners that are capable of obtaining Pap smears, and they recently recruited a midwife to focus specifically on Pap performance. To facilitate the identification of patients who are in need of a Pap smear, the CCC generates a list of such women monthly. This list is circulated to the CCC "Pap Team", a multidisciplinary group of staff members including medical, medical case management, and outreach workers. These staff members each implement various strategies to reach these women and engage them care.

One final tip that the CCC can share, is that looking at patients from a primary care perspective and not just an HIV perspective is an effective way to promote all annual screens. Pap smears are a routine component of their annual preventive screenings, and considered a critical piece of HIV care for women. ❖

The New York/New Jersey AIDS Education and Training Center is now offering a Cervical Pap Test Training Program

Nadine Nader, CQI Manager, NY/NJ AETC

The comprehensive Cervical Pap Test Training Program provides HIV clinicians with the knowledge, skills, and support to conduct cervical Pap tests and pelvic exams for HIV positive women in New Jersey. The objective of the program is to improve rates of cervical Pap tests for HIV positive women.



Who can participate?

- Clinics receiving Ryan White Program Funding
- HIV clinicians interested in the training program that are willing and permitted to perform cervical pap smears in a clinical setting (including physicians, nurse practitioners, physician assistants and nurses)

What type of training is offered to HIV clinicians?

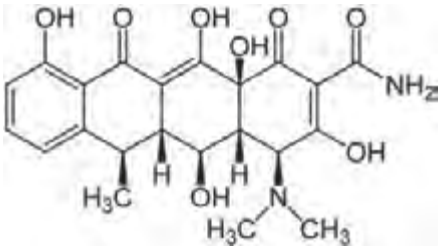
This training program consists of three parts for which continuing education credits are offered by UMDNJ-Center for Continuing and Outreach Education. The training includes an online presentation, a skills-building workshop with simulated patient models, and a clinical training preceptorship. NY/NJ AETC can offer ongoing guidance and technical assistance after completing the training as participants implement cervical screenings in their clinical facility.

> *"The didactic portion and 'hands-on' skills building activity with the anatomical models greatly reduced my anxiety related to providing competent Pap screening services to the HIV positive women in my practice. I am looking forward to the clinical training portion of the program to improve my skills and technique. I am hoping to have an impact on increasing the Pap rates within our clinical site."*
>
> — *Peter Oates RN, MSN, NP-C, ACRN*
> *Manager, Health Care Services*
> *FXB Center, UMDNJ*

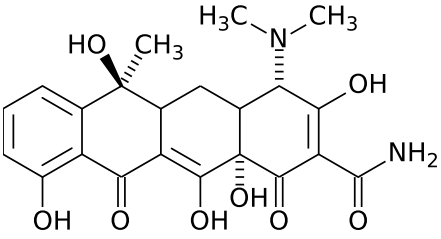
To enroll: Please contact the NY/NJ AETC Central Office by email: *nynjaetc@columbia.edu* or phone: 212-304-5530.

Doxycycline and Tetracycline Shortage Update

In January 2013, the US Food and Drug Administration (FDA) announced a shortage of doxycycline due to manufacturing delays and increased demand. As a result of the shortage, by March prices skyrocketed 14-100 fold from original levels. As of early May there was some improvement: two of the four manufacturers reported that the drug was available and the other two stated that it was in limited supply or that they were experiencing manufacturing delays.



The FDA also reports that tetracycline is unavailable. The FDA Drug Shortage website states that both tetracycline manufacturers (Teva and Watson) have "all tetracycline capsules temporarily unavailable" and "cannot estimate a release date".



Doxycycline is a recommended therapy for some sexually transmitted infections and syndromes including chlamydia, nongonococcal urethritis, epididymitis and pelvic inflammatory disease. It is also an alternative therapy for syphilis in patients with a penicillin allergy. If tetracycline or doxycycline is not available, alternative regimens for sexually transmitted infections are outlined in the table to the right and described in the Center for Disease Control and Prevention's (CDC) 2010 STD Treatment Guidelines. For additional recommendations and alternative regimens for syphilis in nonpregnant patients with a penicillin allergy, please contact a specialist or local health department. ❖

Alternative regimens for STIs

Infection	Regimen
Chlamydia and Nongonococcal urethritis	■ Azithromycin 1 g orally in a single dose
Gonorrhea	■ Ceftriaxone 250 mg IM in a single dose **PLUS** ■ Azithromycin 1 g orally in a single dose
Syphilis (penicillin allergic)*	■ **Primary or secondary syphilis** Tetracycline 500 mg orally four times daily for 14 days **4x/day for 14 days** ■ **Late latent syphilis** Tetracycline 500 mg orally four times daily for 28 days **4x/day for 28 days**
Epididymitis	■ Ceftriaxone 250 mg IM in a single dose **PLUS** ■ Azithromycin 1 g orally in a single dose **PLUS** ■ Levofloxacin 500 mg orally once daily for 10 days
Pelvic Inflammatory Disease**	■ Ceftriaxone 250 mg IM in a single dose **PLUS** ■ Clindamycin 450 mg orally four times daily for 14 days **WITH OR WITHOUT** ■ Metronidazole 500 mg orally twice a day for 14 days

* Pregnant women: Parenteral penicillin G is the only therapy with documented efficacy for syphilis during pregnancy. Pregnant women with syphilis in any stage who report penicillin allergy should be desensitized and treated with penicillin.

** See the CDC's STD Treatment Guidelines for additional regimens (http://www.cdc.gov/std/treatment/2010/)

FDA has listed additional information on manufacturer status regarding the antibiotic, contact information, and other commentary at: http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm

Discovery of a Previously Unknown Bacterium Associated with *Trichomonas vaginalis*

Doctors at Louisiana State University (LSU) Health Sciences Center conducting a study of 400 women attending a sexually transmitted infection (STI) clinic in New Orleans report discovering Mnola, a previously unknown *Mycoplasma* bacterium that is associated with *Trichomonas* vaginalis (trichomonas). Trichomonas is a common STI that is associated with pre-term delivery and increases the risk of HIV infection in women. Women with both trichomonas and *Mycoplasma* bacterial communities have worse disease than women who have only trichomonas, according to Dr. David H. Martin, professor and chief of infectious diseases at LSU's Health Sciences Center. Martin believes the added presence of Mnola makes the risk of HIV higher than infection with trichomonas alone. Another bacterium, *Mycoplasma hominis*, has long been associated with trichomonas. The discovery of Mnola suggested the need to reexamine the relationship of vaginal *Mycoplasma* bacteria communities with trichomonas.

Dr. David H. Martin, professor and chief of infectious diseases at LSU's Health Sciences Center

Trichomonas vaginalis

Whereas the researchers once thought that the presence of vaginal bacterial colonies predisposed women to infection with trichomonas, the team now believes that trichomonas is responsible for the appearance of *Mycoplasma*-dominated bacterial communities. Martin theorizes that trichomonas actually "cultivates" Mnola and *Mycoplasma hominis* because the Mycoplasma communities somehow benefit the parasite. Future research will focus on how Mnola interacts with trichomonas and whether trichomonas is responsible for the appearance of the vaginal bacterial colonies. Vaginal discharge and redness of the vaginal wall can be symptoms of infection, but some women are asymptomatic. ❖

Source of summary: National Prevention Information Network. http://www.cdcnpin.org/scripts/display/NewsDisplay.asp?NewsNbr=61368

Full report: Martin, DH., Zozaya, M., Lillis, RA., et al. "Unique vaginal microbiota which include an unknown Mycoplasma-like organism are associated with Trichomonas vaginalis infection." ***J Infect Dis.*** (2013) doi: 10.1093/infdis/jit100. First published online: March 12, 2013. Available at: http://jid.oxfordjournals.org/content/early/2013/03/12/infdis.jit100.full.pdf+html

Pediatric HIV Drug Gains FDA Approval

SUSTIVA® (generic name: efavirenz) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that was originally approved in the U.S. in 1998 to treat HIV-1 infected adults and children three years of age or older and weighing at least 10 kg. In May 2013, Bristol-Myers Squibb Company received U.S. Food and Drug Administration (FDA) approval of SUSTIVA for the treatment of HIV-infected pediatric patients three months to three years of age and weighing at least 3.5 kg.

Recommended dosing of SUSTIVA

Body weight	Daily dose	Number of capsules or tablets and strength to administer
3.5 to less than 5 kg	100 mg	Two 50-mg capsules
5 to less than 7.5 kg	150 mg	Three 50-mg capsules
7.5 to less than 15 kg	200 mg	One 200-mg capsule
15 to less than 20 kg	250 mg	One 200-mg + one 50-mg capsule
20 to less than 25 kg	300 mg	One 200-mg + two 50-mg capsules
25 to less than 32.5 kg	350 mg	One 200-mg + three 50-mg capsules
32.5 to less than 40 kg	400 mg	Two 200-mg capsules
At least 40 kg	600 mg	One 600-mg tablet or three 200-mg capsules

This approval offers a once-daily option as part of a regimen for this population and includes a "capsule sprinkle" administration method for patients who cannot swallow capsules or tablets. Detailed information about the "capsule sprinkle" method is provided in the "Instructions for Use" at the end of the Patient Information section of the Package Insert (available at: *http://packageinserts.bms.com/pi/pi_sustiva.pdf*).

Approval of Crofelemer to Relieve Symptoms of Diarrhea

Many people with HIV experience diarrhea that can lead to discontinuation or switching of their antiretroviral therapy (ART) regimen. On December 31, 2012, FDA approved crofelemer (brand name: Fulyzaq) to relieve symptoms of diarrhea in people with HIV taking ART. Crofelemer is indicated in HIV patients whose diarrhea is not caused by an infection from a virus, bacteria, or parasite.

Safety and efficacy of crofelemer were established in placebo-controlled trials.

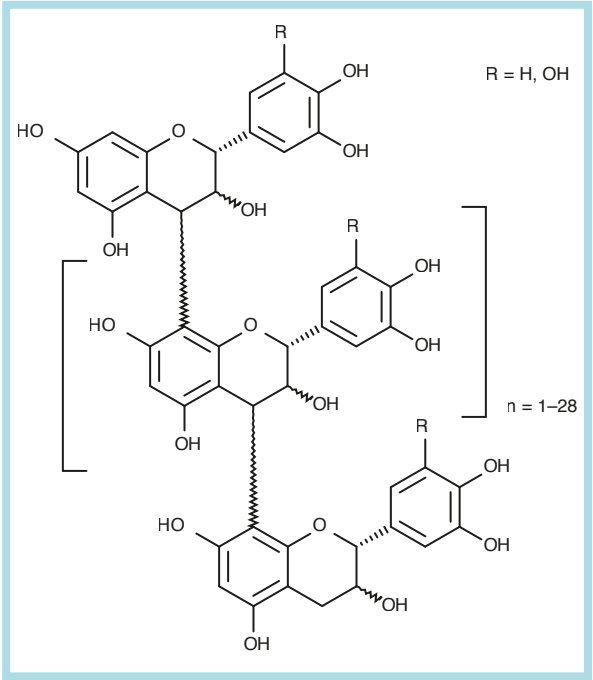
In a placebo-controlled trial that included 374 patients on ART with a history of diarrhea lasting one month or longer, the median number of daily watery bowel movements at the start of the study was 2.5 per day. Patients who had diarrhea caused by an infection or a gastrointestinal disease were excluded from participating in the trials. Patients were randomly assigned to take crofelemer or a placebo twice daily.

The trial was designed to measure clinical response, defined as the number of patients who had two or fewer watery bowel movements weekly. Results showed that 17.6 percent of patients taking crofelemer experienced clinical response compared with 8 percent taking placebo. In some patients, a persistent antidiarrheal effect was seen for 20 weeks. The safety and effectiveness of crofelemer have not been established in pediatric patients less than 18 years of age.

Use of crofelemer

Before treating patients with crofelemer, healthcare professionals should conduct testing to confirm the diarrhea is not caused by an infection or a gastrointestinal disease. If infectious etiologies are not considered, and crofelemer is initiated based on a presumptive diagnosis of non-infectious diarrhea, then there is a risk that patients with infectious etiologies will not receive the appropriate treatments, and their disease may worsen.

The recommended dose is one 125 mg delayed-release tablet taken orally two times a day, with or without food. Common side effects reported in patients taking crofelemer in the clinical trial were upper respiratory tract infection, bronchitis, cough, flatulence, and increased levels of the liver enzyme bilirubin. The product label for crofelemer can be found at *Drugs@FDA* (*http://www.accessdata.fda.gov/scripts/cder/drugsatfda/*)❖



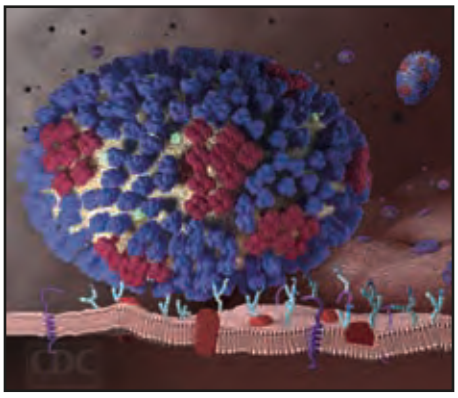
Research Supports High-Dose Flu Vaccine for People with HIV

(Original article written by Don Sapatkin, Philadelphia Inquirer Staff Writer, posted January 3, 2013.)

The elderly and people with compromised immune systems account for the vast majority of the thousands of deaths from seasonal influenza. They get sicker and are more likely to experience serious complications. They also produce a weaker response to standard vaccine, making them more likely to catch the flu.

In late 2009, the FDA licensed Fluzone High-Dose, made by Sanofi Pasteur, for use in people 65 and older. It wasn't until earlier this year that evidence became available indicating that Fluzone High-Dose is also effective in building a higher immune response among HIV-infected people. The University of Pennsylvania study — funded by the National Institutes of Health, not the Fluzone High-Dose maker Sanofi Pasteur — compared the immune response of HIV-infected people who received the standard dose of Fluzone with a group of HIV-infected people who took Fluzone High-Dose. The Fluzone High-Dose group developed more antibodies to the flu and had an immunization response more like healthy younger adults. It was not clear from the results of the study whether people with AIDS (CD4 counts under 200) would receive the same immunization benefit from Fluzone High-Dose.

At present, the FDA has only approved Fluzone High-Dose for use with people 65 and older. It is unlikely that insurance companies would reimburse the use of Fluzone High-Dose with HIV-infected people unless the immunization practices committee of the Centers for Disease Control and Prevention (CDC) recommends this additional use. There must be a "compelling reason" for CDC to endorse a use other than that approved by the FDA, said CDC's Jean Clare Smith, MD. Researchers will request that CDC review the study and recommend the use of Fluzone High-Dose with HIV-infected people. ❖



An Influenza Virus Binds to a Respiratory Tract Cell. *http://www.cdc.gov/flu/images.htm*

The full report, "Improved Immunogenicity with High-Dose Seasonal Influenza Vaccine in HIV-Infected Persons: A Single-Center, Parallel, Randomized Trial," was published in the *Journal Annals of Internal Medicine* (2013; 158(1):19-26).

KEEP YOUR CUP EMPTY.

Compassion Fatigue in the 4th Decade of HIV

David Rubenstein, Psy.D., M.S.W, Senior Director for Student Wellness at Rowan University and Adjunct Clinical Associate Professor of Psychiatry at Drexel University College of Medicine

"Compassion Fatigue"… such an interesting combination of words to put together. When we think of compassion, we think of an endless supply of goodwill, empathy, caring, sensitivity, humility all wrapped up into one way of being towards another human being. When we think of fatigue, we think of the awareness of approaching our limit, reaching a place where we can no longer express the expenditure of energy we once could — whether it be physical, emotional, or psychological. Compassion fatigue suggests that we have given our best… and we are drained. We are committed to return… maybe… just not sure when.

In the world of HIV work, there is no shortage of compassion and compassionate providers. HIV providers demonstrate dedication, commitment, fortitude, compassion, caring and skill. HIV is now entering into its fourth decade — after emerging on the scene in this country in the early 1980s. Many HIV providers have been in the field just as long, committed to fairness, justice, and equality of care from the beginning; continuing to demonstrate commitment to delivering the best care possible with the awareness of ever-dwindling resources.

It is not uncommon for individuals living with HIV to experience feelings related to isolation, stigma, shame, humiliation, and fears around sharing their health issues with others. Some also have to cope with co-occurring mental health and substance abuse issues. These internal experiences — coupled with trying to manage the multitude of environmental and current economic stressors — are often what many individuals living with HIV bring when then come into care. For the patient that is coming into treatment, having weathered the lonely

experience of what feels like a never ending storm, the HIV clinic is a safe harbor, and you as provider, a safe buoy to connect with.

This is where the emergence of compassion fatigue comes into play. The treatment environment contains a never-ending ebb and flow of individuals who come into care, sometimes with great suffering, and in need of much attention. Caring for these individuals are providers who face the reality of working with limited clinic resources, and limited city, county, state, regional and national resources. You, as the provider, take great care to identify the individual's needs, whether medical, psychological, social, environmental, or financial and give your best to meet these needs. The experience of the endless giving of attention, care, skill, empathy, problem-solving, and crisis-management in a larger environment that has less and less available, requires you to rely more on what you can offer of yourself — compassion. Whether you like it or not, you have your limits.

Recognizing compassion fatigue can be a lonely and brave personal experience, one that is difficult to come to terms with, but necessary. The price of avoidance will be a loss in your own skills as a provider, skills fortified by compassion. Identifying the source(s) of compassion fatigue is critical to remedying the situation. The source can be from one area or from many different areas. They can range from invalidating work environments, to insufficient resources for patients, insufficient staffing resources, insufficient supervision, lack of compensation, insufficient professional development opportunities, inflexible policies and procedures, or difficult work-relationships. Maxwell (1993) suggests, in terms of recognizing problem areas in your work environment, use your intuition as a guide:

- Ask questions and get the facts
- Share feelings and findings with colleagues you trust
- Define the problem further and check your resources for handling the problem
- Develop solutions and prioritize
- Decide how you will handle the problem

Symptoms of compassion fatigue can show up in many areas and, paradoxically can be expressed as:

- Impatience
- Insensitivity
- Rushed decision-making
- Lack of empathy
- Unwarranted expressions of frustration with your patients and co-workers

Unfortunately, attempting to push through compassion fatigue, can have the impact of further depleting personal reserves and this can affect your own mood and overall level of functioning in personal relationships, family relationships, motivation, energy level, sleep, or appetite. Tending to yourself and coping and repairing your personal and professional sense of self is what is required. This could mean:

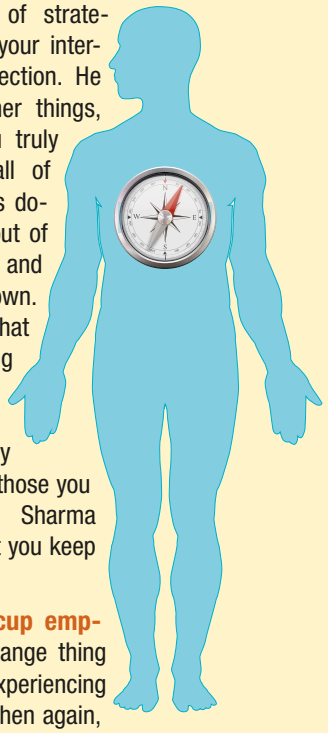
- That you simply need to pull over at the side of the road so you can catch your breath, or
- That you need to address specific clinic and or organizational issues that are impacting your work, or
- That you need to reevaluate the kind of work you are doing and reassess if it fits developmentally with what is wanted and needed in life, personally and/or professionally

In caring for yourself, Fox (1998) recommends activities to put yourself at the forefront. These activities include:

- Keeping physically fit
- Doing something hard and lonely
- Spending one hour each day planning, dreaming, calculating, thinking, scheming (positively)
- Using a "special idea" notebook
- Not taking work home
- Not hiding the white elephant
- Always taking vacations
- Going to the library once per month
- Trying to never panic or lose your temper
- Treating all people as special
- Being polite with everyone
- Having fun and laughing
- Treating your family as your number one client

This is a wonderful list of personal ideals and activities to ascribe to in both preventing and working though compassion fatigue.

For those individuals who find themselves in the place of being unsure if the work they are doing is still right for them, Sharma (1997) suggests a number of strategies towards finding your internal compass and direction. He suggests, among other things, finding out what you truly love and directing all of your energies towards doing it, daring to get out of your circle of comfort and exploring the unknown. Sharma concludes that when you are doing what you truly love to do you will find deep contentment; the only limits on your life are those you set yourself. Finally, Sharma also recommends that you keep your cup empty.



Yes… "keep your cup empty," seems like a strange thing to do for a person experiencing compassion fatigue. Then again, keeping your cup empty means making sure you keep searching and finding what is most important to you no matter where you are in your personal and professional life. Living this kind of life, you will always be drinking from the Well and you will have all the energy you need to find the life worth searching for.

Dr. Rubenstein has been working with patients since 1987. He has worked with mental health, substance abuse and HIV/AIDS patients in both outpatient and inpatient medical, mental health, and substance abuse settings. ❖

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www.fxbcenter.org
www.umdnj.edu/ccoe
http://www.state.nj.us/health/aids/index.shtml

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NJDOH-DHSTS New Jersey AIDS Drug Distribution Program and Health Insurance Continuation Program eligibility, application and recertification Podcast.
http://hpcpsdi.rutgers.edu/training/main.php

NY/NJ AETC Cervical Pap Test Training Program for Clinical Providers in New Jersey
A CME/CE program developed to provide HIV clinicians with the knowledge, skills, and support to perform cervical Pap tests and pelvic exams for HIV-positive women as recommended by national guidelines, to reduce the barriers for clinicians and patients associated with lower cervical Pap test rates, and ultimately, to improve Pap test clinical rates. For more information: 212-304-5530 or http://www.nynjaetc.org/on-demand/cervicalpapprogram.html

HIV/AIDS Training & Information Resources

New Jersey Department of Health – Division of HIV, STD and TB Services (NJDOH-DHSTS) • (609) 984-5874 • www.state.nj.us/health/aids
- NJ HIV/AIDS statistical reports, regulations, forms, and links to HIV care, prevention programs, and training
- New Jersey rapid testing site: www.state.nj.us/health/aids/rapidtesting
- New Jersey AIDS/STD Hotline: (800) 624-2377

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http://www.fxbcenter.org/
- HIV/AIDS conferences, training
- Free online continuing education (CE) credits for healthcare professionals
- HIV/AIDS MEDICAL UPDATE SERIES: with funding from NJDOH
- Free on-site HIV medical education for healthcare sites.
- Contact Michelle Thompson at (973) 972-1293 or ccthomps@umdnj.edu

AIDS Education and Training Centers (AETC) National Resource Center:
www.aidsetc.org
- NY/NJ AETC: www.nynjaetc.org

AIDS InfoNet: HIV treatment fact sheets in English and 10 other languages.
www.aidsinfonet.org

AIDSinfo: a service of the U.S. Department of Health and Human Services (HHS), offers access to the latest, federally approved HIV/AIDS medical practice guidelines, HIV treatment and prevention clinical trials, and other research information.
http://www.aidsinfo.nih.gov/

ClinicalTrials.gov: Web-based resource that provides easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions.
http://clinicaltrials.gov

Centers for Disease Control (CDC):
Key HIV/AIDS resources.
www.cdc.gov/hiv/hivinfo.htm#WWW

Health Resources and Services Administration (HRSA): http://www.hrsa.gov and http://hab.hrsa.gov

FDA MedWatch: (800) FDA-1088; Subscribe to e-bulletin:
www.fda.gov/medwatch/elist.htm

HealthHIV: Advances effective prevention, care and support for people living with, or at risk for, HIV/AIDS by providing education, capacity building, health services research, and advocacy.
http://www.healthhiv.org/index.php

National HIV/AIDS Clinicians' Consultation Center:
http://www.nccc.ucsf.edu/
- Warmline: (800) 933-3413
- Post-Exposure Prophylaxis Hotline/PEPline: (888) 448-4911
- Perinatal HIV Hotline: (888) 448-8765

National Quality Center: Provides no-cost, technical assistance for Ryan White funded grantees to improve the quality of HIV care nationwide.
www.nationalqualitycenter.org

TARGET Center: Technical assistance and training resources for the Ryan White HIV/AIDS Program.
www.careacttarget.org

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